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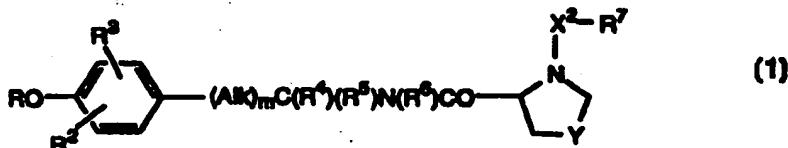
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(54) Title: ANTI-INFLAMMATORY TYROSINE DERIVATIVES



(57) Abstract

Tyrosine derivatives of formula (1) are described in which R is (1) a group R^1X^1L where R^1 is an optionally substituted alkyl or aromatic group, and X^1 is a covalent bond or a $-(CH_2)_n-$ (where n is an integer 1 or 2), $-C(O)-$, $-CH_2CO-$, $-NHC(O)-$, $-CH_2NHC(O)-$, or $-SO_2-$ group, or (2) a group $(Hal^1)_2CSO_2-$, where Hal^1 is a fluorine or chlorine atom; R^2 and R^3 , which may be the same or different, is each a hydrogen or halogen atom or an alkyl, alkoxy, hydroxyl or nitro group; Alk is an alkylene chain; m is zero or an integer 1; R^4 is a hydrogen atom or a methyl group; R^5 is a group $-(CH_2)_pCO_2R^8$ where p is zero or an integer 1 and R^8 is a hydrogen atom or an alkyl group; R^6 is a hydrogen atom or an alkyl group; Y is a sulphur atom or a $-S(O)q-$ group where q is an integer 1 or 2; X^2 is a $-C(O)-$, $-C(O)O-$, $-CONH-$ or $-S(O)_2-$ group; R^7 is an optionally substituted alkyl group or an aryl or aralkyl group; and the salts, solvates and hydrates thereof. The compounds are able to inhibit the binding of α_4 integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders.

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ANTI-INFLAMMATORY TYROSINE DERIVATIVES

This invention relates to a series of tyrosine derivatives, to compositions containing them, to processes for their preparation, and to their use in medicine.

Over the last few years it has become increasingly clear that the physical interaction of inflammatory leukocytes with each other and other cells of the body plays an important role in regulating immune and inflammatory responses [Springer, T A. *Nature*, 346, 425, (1990); Springer, T. A. *Cell* 76, 301, (1994)]. Many of these interactions are mediated by specific cell surface molecules collectively referred to as cell adhesion molecules.

The adhesion molecules have been sub-divided into different groups on the basis of their structure. One family of adhesion molecules which is believed to play a particularly important role in regulating immune and inflammatory responses is the integrin family. This family of cell surface glycoproteins has a typical non-covalently linked heterodimer structure. At least 14 different integrin alpha chains and 8 different integrin beta chains have been identified [Sonnenberg, A. *Current Topics in Microbiology and Immunology*, 184, 7, (1993)]. The members of the family are typically named according to their heterodimer composition although trivial nomenclature is widespread in this field. Thus the integrin termed $\alpha 4\beta 1$ consists of the integrin alpha 4 chain associated with the integrin beta 1 chain, but is also widely referred to as Very Late Antigen 4 or VLA4. Not all of the potential pairings of integrin alpha and beta chains have yet been observed in nature and the integrin family has been subdivided into a number of subgroups based on the pairings that have been recognised [Sonnenberg, A. *ibid*].

The importance of cell adhesion molecules in human leukocyte function has been further highlighted by a genetic deficiency disease called Leukocyte Adhesion Deficiency (LAD) in which one of the families of leukocyte integrins is not expressed [Marlin, S. D. et al *J. Exp. Med.* 164, 855 (1986)]. Patients with this disease have a reduced ability to recruit

leukocytes to inflammatory sites and suffer recurrent infections which in extreme cases may be fatal.

5 The potential to modify adhesion molecule function in such a way as to beneficially modulate immune and inflammatory responses has been extensively investigated in animal models using specific monoclonal antibodies that block various functions of these molecules [e.g. Issekutz, T. B. J. Immunol. 3394, (1992); Li, Z. et al Am. J. Physiol. 263, L723, (1992); Binns, R. M. et al J. Immunol. 157, 4094, (1996)]. A number of 10 monoclonal antibodies which block adhesion molecule function are currently being investigated for their therapeutic potential in human disease.

15 One particular integrin subgroup of interest involves the $\alpha 4$ chain which can pair with two different beta chains $\beta 1$ and $\beta 7$ [Sonnenberg, A. *ibid*]. The $\alpha 4\beta 1$ pairing occurs on many circulating leukocytes (for example lymphocytes, monocytes and eosinophils) although it is absent or only present at low levels on circulating neutrophils. $\alpha 4\beta 1$ binds to an adhesion molecule (Vascular Cell Adhesion Molecule-1 also known as VCAM-1) 20 frequently up-regulated on endothelial cells at sites of inflammation [Osborne, L. Cell, 62, 3, (1990)]. The molecule has also been shown to bind to at least three sites in the matrix molecule fibronectin [Humphries, M. J. et al. Ciba Foundation Symposium, 189, 177, (1995)]. Based on data obtained with monoclonal antibodies in animal models it is believed 25 that the interaction between $\alpha 4\beta 1$ and ligands on other cells and the extracellular matrix plays an important role in leukocyte migration and activation [Yednock, T. A. et al, Nature, 356, 63, (1992); Podolsky, D. K. et al. J. Clin. Invest. 92, 373, (1993); Abraham, W. M. et al. J. Clin. Invest. 93, 776, (1994)].

30 The integrin generated by the pairing of $\alpha 4$ and $\beta 7$ has been termed LPAM-1 [Holzmann, B and Weissman, I. EMBO J. 8, 1735, (1989)] and like $\alpha 4\beta 1$, binds to VCAM-1 and fibronectin. In addition, $\alpha 4\beta 7$ binds to an adhesion molecule believed to be involved in the homing of leukocytes to 35 mucosal tissue termed MAdCAM-1 [Berlin, C. et al, Cell, 74, 185, (1993)]. The interaction between $\alpha 4\beta 7$ and MAdCAM-1 may also be important at

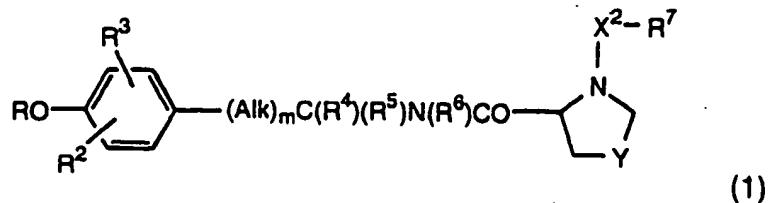
sites of inflammation outside of mucosal tissue [Yang, X-D. *et al*, PNAS, 91, 12604 (1994)].

Regions of the peptide sequence recognised by $\alpha 4\beta 1$ and $\alpha 4\beta 7$ when they bind to their ligands have been identified. $\alpha 4\beta 1$ seems to recognise LDV, IDA or REDV peptide sequences in fibronectin and a QIDSP sequence in VCAM-1 [Humphries, M. J. *et al*, *ibid*] whilst $\alpha 4\beta 7$ recognises a LDT sequence in MAdCAM-1 [Briskin, M. J. *et al*, *J. Immunol.* 156, 719, (1996)]. There have been several reports of inhibitors of these interactions being designed from modifications of these short peptide sequences [Cardarelli, P. M. *et al* *J. Biol. Chem.* 269, 18668, (1994); Shroff, H. N. *Bioorganic. Med. Chem. Lett.* 6, 2495, (1996); Vanderslice, P. J. *Immunol.* 158, 1710, (1997)]. It has also been reported that a short peptide sequence derived from the $\alpha 4\beta 1$ binding site in fibronectin can inhibit a contact hypersensitivity reaction in a trinitrochlorobenzene sensitised mouse [Ferguson, T. A. *et al*, *PNAS* 88, 8072, (1991)].

Since the alpha 4 subgroup of integrins are predominantly expressed on leukocytes, inhibition of their ligand binding abilities can be expected to be beneficial in a number of immune or inflammatory disease states. However, because of the ubiquitous distribution and wide range of functions performed by other members of the integrin family it is very important to be able to identify inhibitors which will selectively inhibit the binding of the alpha 4 subgroup.

We have now found a group of compounds which are potent and selective inhibitors of the binding of $\alpha 4$ integrins to their ligands. Members of the group are able to inhibit the binding of $\alpha 4$ integrins such as $\alpha 4\beta 1$ and/or $\alpha 4\beta 7$ to their ligands at concentrations at which they generally have no or minimal inhibitory action on α integrins of other subgroups. The compounds are thus of use in medicine, for example in the prophylaxis and treatment of immune or inflammatory disorders as described hereinafter.

Thus according to one aspect of the invention we provide a compound of formula (1)



wherein

- 5 R is (1) a group R^1X^1 - where R^1 is an optionally substituted alkyl or aromatic group, and X^1 is a covalent bond or a $-(CH_2)_n-$ [where n is an integer 1 or 2], $-C(O)-$, $-CH_2C(O)-$, $-NHC(O)-$, $-CH_2NHC(O)-$, or $-SO_2-$ group, or (2) a group $(Hal^1)_3CSO_2-$, where Hal^1 is a fluorine or chlorine atom;
- 10 R² and R³, which may be the same or different, is each a hydrogen or halogen atom or an alkyl, alkoxy, hydroxyl or nitro group;
Alk is an alkylene chain;
m is zero or an integer 1;
R⁴ is a hydrogen atom or a methyl group;
- 15 R⁵ is a group $-(CH_2)_pCO_2R^8$ where p is zero or an integer 1 and R⁸ is a hydrogen atom or an alkyl group;
R⁶ is a hydrogen atom or an alkyl group;
Y is a sulphur atom or a $-S(O)q-$ group where q is an integer 1 or 2;
X² is a $-C(O)-$, $-C(O)O-$, $-CONH-$ or $-S(O)_2-$ group;
- 20 R⁷ is an optionally substituted alkyl group or an aryl or aralkyl group;
and the salts, solvates and hydrates thereof.

It will be appreciated that compounds of formula (1) may have one or more chiral centres. Where one or more chiral centres is present, enantiomers

- 25 or diastereomers may exist, and the invention is to be understood to extend to all such enantiomers, diasteromers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise.

30

In the compounds of formula (1), when the group R¹ is an optionally substituted alkyl group it may be for example an optionally substituted

straight or branched chain C₁-alkyl group such as an optionally substituted methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group. Optional substituents which may be present on such groups include one, two or three halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl or C₁-alkoxy e.g. methoxy or ethoxy groups.

5 straight or branched chain C₁-alkyl group such as an optionally substituted methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group. Optional substituents which may be present on such groups include one, two or three halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl or C₁-alkoxy e.g. methoxy or ethoxy groups.

10 Optionally substituted aromatic groups represented by the group R¹ in compounds of formula (1) include for example optionally substituted monocyclic or bicyclic fused ring C₆-12 aromatic groups, such as optionally substituted phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups .

15 Optional substituents which may be present on aromatic groups of this type include one, two, three or more substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C₁-alkyl, e.g. methyl or ethyl, C₁-alkoxy, e.g. methoxy or ethoxy, hydroxyl, -NH₂, -NHCOCH₃ or nitro groups. Each of said alkyl or alkoxy groups may be optionally substituted by one, two or three halogen atoms, for example fluorine, chlorine, bromine or iodine atoms, and/or hydroxyl groups.

20 Particular examples of substituted alkyl and alkoxy groups include -CF₃, -OCF₃, -CHF₂, -OCHF₂, -CH₂F, -OCH₂F, -CH₂OH, -(CH₂)₂OH, -O(CH₂)₂OH and -C(OH)(CF₃)₂ groups.

25 Alkyl groups represented by the groups R², R³, R⁶ and/or ,when present, R⁸ in compounds of the invention include for example straight or branched C₁-alkyl groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl groups.

30 Alkoxy groups represented by the groups R² and/or R³ include straight or branched C₁-alkoxy groups such as methoxy or ethoxy groups.

The alkylene chain represented by Alk in compounds of formula (1) may be for example a straight or branched C₁-3alkylene chain such as a -CH₂-, -(CH₂)₂- or -CH(CH₃)- chain.

Optionally substituted alkyl groups represented by the group R⁷ in compounds of the invention include optionally substituted straight or branched C₁-C₆alkyl groups such as optionally substituted methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl groups. Optional substituents which may be present on these groups include one, two or three substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl, C₁-C₄alkoxy, e.g. methoxy or ethoxy, -CO₂H, amino (-NH₂), C₁-C₆alkylamino, e.g. methylamino (-NHCH₃) or ethylamino, C₁-C₆dialkylamino e.g. dimethylamino or diethylamino, -NHCOCH₃ or -NHCO₂R¹⁰ group in which R¹⁰ is a hydrogen atom or a straight or branched C₁-C₄alkyl group such as a methyl, ethyl, i-propyl or t-butyl group.

When in the compounds of the invention the group R⁷ is an aryl group it may be for example an optionally substituted monocyclic or bicyclic fused ring C₆-C₁₂aromatic group as described above for the group R¹.

When in the compounds of formula (1) R⁷ is an aralkyl group it may be for example an optionally substituted monocyclic or bicyclic fused ring C₆-C₁₂aromatic-C₁-C₃alkylene group. In groups of the type the aromatic portion may in particular be an optionally substituted aromatic group as described above for the group R¹. The C₁-C₃alkylene portion may be for example a methylene or ethylene chain. Particular examples of aralkyl groups include optionally substituted benzyl groups.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example salts derived from inorganic and organic bases. Particular examples of such salts include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

One particular class of compounds according to the invention has the formula (1) wherein R⁴ is a hydrogen atom and the remaining groups are

as defined above for formula (1) and the salts, solvates and hydrates thereof.

5 In another class of compounds of formula (1) the group R⁵ is a -CH₂CO₂H group, or in particular is a -CO₂H group.

In compounds of this class, and in general in compounds of formula (1) Y is preferably a sulphur atom.

10 In another general preference, m in compounds of formula (1) is the integer 1 and Alk in particular is a -CH₂- chain. In compounds of this type, and when R⁵ is a -CO₂H group, the carbon atom to which R⁵ and Alk are attached forms a chiral centre and is preferably in the L configuration.

15 The group R in compounds of formula (1) is preferably a R¹X¹- group. In compounds of this type R¹ is preferably an optionally substituted phenyl group. Particularly useful groups of this type include mono-, di- or trisubstituted phenyl groups. The substituent(s) may be located on any available carbon atom in the phenyl ring at the 2-, 3-, 4-, 5- and 6-positions

20 relative to the point of attachment of the phenyl group to the remainder of the molecule of formula (1). Thus, for example when more than one substituent is present, the substituents may be located at the 2,6- and 2, 4, 6- positions. Particularly useful substituents include halogen atoms such as chlorine and fluorine atoms. X¹ in compounds of these particular types is preferably a -CH₂- or -C(O)- group.

R⁶ in compounds of formula (1) may for example be a methyl group or in particular a hydrogen atom.

30 X² in the compounds according to the invention is preferably a -C(O)- group.

The group R⁷ in the compounds according to the invention may in particular be an optionally substituted C₁-3alkyl or benzyl group.

35 Optionally substituted C₁-3alkyl groups are especially useful, and in particular R⁷ is preferably a methyl group.

Particularly useful compounds according to the invention includ :

N-Acetyl-*D*-thioproline-(O-2,6-dichlorobenzyl)-*L*-tyrosin ;

N-Acetyl-*D*-thioproline-(O-2,4,6-trichlorobenzyl)-*L*-tyrosine;

5 *N*-Acetyl-*D*-thioproline-(O-2,6-difluorobenzyl)-*L*-tyrosine;

N-Acetyl-*D*-thioproline-(O-2,6-dichlorobenzyl)-3-nitro-*L*-tyrosine;

N-(3-Carboxy)propionyl-*D*-thioproline-(O-2,6-dichlorobenzyl)-*L*-tyrosine;

N-Acetyl-*D*-thioproline-(O-2,4,6-trichlorobenzoyl)-*L*-tyrosine

and the salts, solvates and hydrates thereof.

10

Compounds according to the invention are potent and selective inhibitors of the binding of $\alpha 4$ integrins to their ligands. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

15

The compounds are of use in modulating cell adhesion and in particular are of use in the prophylaxis and treatment of diseases or disorders involving inflammation in which the extravasation of leukocytes plays a role. The Invention extends to such uses and to the use of each

20 compound for preparing a medicament for treating these diseases and disorders. Particular Diseases or disorders of this type include inflammatory arthritis such as rheumatoid arthritis vasculitis or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes,

25 inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease. The compounds may also be useful for modulating the circulating levels of early haematopoichic cells, such as stem cells to enable their collection for e.g. bone marrow transplantation.

30 For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

- 5 For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

- 25 For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

- 30 The compounds for formula (1) may be formulated for parenteral administration by injection including by bolus injection or infusion or particle mediated injection. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials or a device containing a compressed gas such as helium for particle mediated administration. The compositions for bolus injection or infusion may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively,
- 35

the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. For particle mediated administration the active ingredient may be coated on particles such as microscopic gold particles.

5

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

10

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichloro-

15

fluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

20

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general,

25

however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg

30

to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols R,

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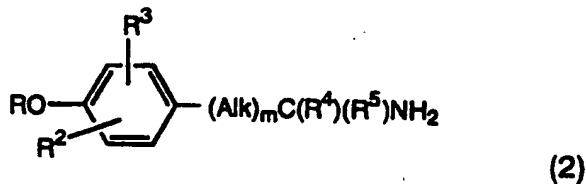
R¹-R⁷, Alk, m, Y and X¹ when used in the formulae depicted are to be

understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy or carboxy groups, where these are desired in the final product, to

- 5 avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes
- 10 according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

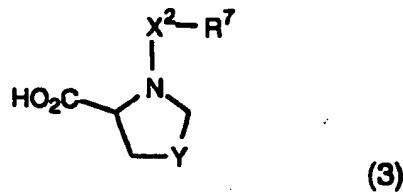
Thus according to a further aspect of the invention, a compound of formula (1) wherein R⁵ is a group -(CH₂)_pCO₂R⁸ in which p is zero or an integer 1

- 15 and R⁸ is an alkyl group may be prepared by coupling an amine of formula (2):



(where R⁵ is as just described) or a salt thereof with an acid of formula (3):

20



or an active derivative thereof.

- 25 Active derivatives of acids of formula (3) include anhydrides, esters and halides. Particular esters include pentafluorophenyl or succinyl esters.

The coupling reaction may be performed using standard conditions for reactions of this type. Thus for example the reaction may be carried out in a solvent, for example an inert organic solvent such as an amide, e.g. a

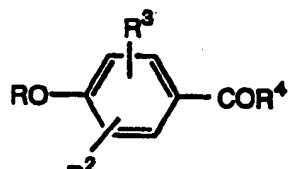
substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran, or a halogenated hydrocarbon, such as dichloromethane, at a low temperature, e.g. around -30°C to around ambient temperature, optionally in the presence of a base, e.g. an organic base such as an amine, e.g. triethylamine, pyridine, or a cyclic amine, such as N-methylmorpholine.

5

Where an acid of formula (3) is used, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide 10 such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively, the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to reaction with the amine of formula 15 (2).

Intermediate amines of formula (2) wherein R⁵ is a group -CO₂R⁸ are either known compounds or may be prepared from known starting materials by methods analogous to those used for the preparation of the 20 known compounds. Where appropriate, standard substitution approaches such as those described below employing for example alkylation, arylation, acylation, halogenation, sulphonylation, nitration or coupling reactions may be used to obtain new R, R², R³ or R⁵ substituents in known amines of formula (2). In these reactions the amine may need to be suitably 25 protected, for example as described by Green, T. W. *ibid.*

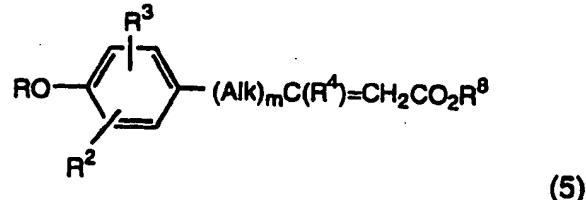
Intermediate amines of formula (2) wherein m is zero and R⁵ is a group -CH₂CO₂R⁸ may be prepared by reaction of an aldehyde or ketone of formula (4):



30

with malonic acid and ammonia or an ammonium salt, e.g. ammonium acetate, in the presence of a base, followed by reaction with an alcohol R⁸OH in the presence of an acid such as hydrochloric acid.

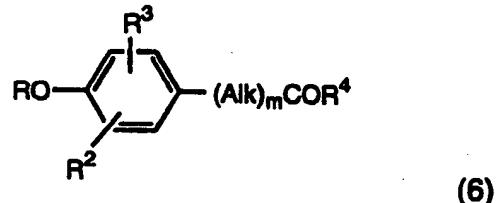
5 Intermediate amines of formula (2) wherein R⁵ is a group -CH₂CO₂R⁸ may be prepared by reaction of an α,β-unsaturated ester of formula (5):



with benzylamine or a substituted benzylamine, optionally in the presence of a base, followed by hydrogenation using for example hydrogen or a

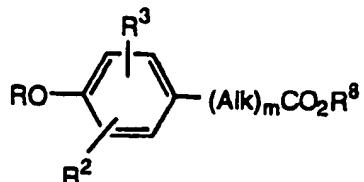
10 hydrogen donor such as formic acid and a transfer agent such as a metal catalyst, for example palladium on a support such as carbon in a solvent such as methanol at an ambient or elevated temperature.

15 The esters of formula (5) may be obtained by reaction of an aldehyde or - ketone of formula (6):



20 with a phosphonium salt (R⁹)₃P+CH₂CO₂R⁸Hal⁻ (where Hal is a halogen atom and R⁹ is for example a phenyl group) or a stabilised ylide (R⁹)₃P=CHCO₂R⁸ in the presence of a base such as sodium ethoxide in a solvent such as ethanol or phenyllithium in a solvent such as tetrahydrofuran at around ambient temperature.

25 Aldehydes of formula (6) wherein R⁴ is a hydrogen atom may be prepared by reduction of a corresponding ester of formula (7):

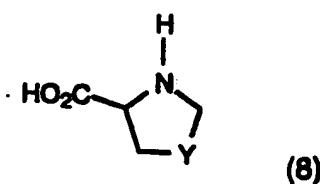


5 (where R^8 is an alkyl group) using a reducing agent such as a metal hydride, e.g. diisobutylaluminium hydride, at a low temperature e.g. around -78°C in an organic solvent such as toluene.

10 Ketones of formula (6) wherein R^4 is a methyl group may be prepared by treating a corresponding aldehyde of formula (6) with a Grignard reagent such as methylmagnesium bromide, or methyl lithium in a solvent such as tetrahydrofuran, at a low temperature e.g. around -55°C to 0°C and oxidising the resulting alcohol using an oxidising agent such as manganese dioxide.

15 Intermediate aldehydes and ketones of formula (4) and intermediate esters of formula (7) are either known compounds or may be prepared from known starting materials by methods analogous to those used for the preparation of the known compounds, where appropriate employing standard substitution approaches to obtain any desired R , R^2 , R^3 and/or R^8 group as described above in relation to the intermediate amines of formula (2).

20 The acids of formula (3) for use in the preparation of compounds of the invention are also either known compounds or may be prepared from known starting materials by use of analogous processes to those used for the preparation of the known compounds, for example by acylation or sulphonylation of an acid of formula (8):



or a protected derivative thereof using for example a reagent R^7COHal , R^7CO_2H , R^7SO_2Hal or R^7NCO and standard conditions for reactions of this type such as those described hereinafter for the functionalisation of phenols of formula (9).

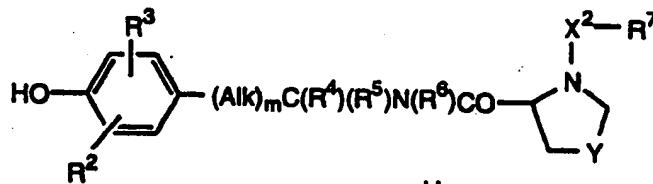
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In another aspect of the invention a compound of formula (1) may be obtained from a corresponding compound of formula (1) via an interconversion process.

- 10 Thus, in one particular example, a compound of formula (1) wherein R^5 is a $-CO_2H$ or $-CH_2CO_2H$ group may be obtained by hydrolysis of a corresponding ester wherein R^5 is a $-CO_2R^8$ or $-CH_2CO_2R^8$ group and R^8 is an alkyl group. The hydrolysis may be performed using either an acid or a base depending on the nature of the ester starting material, for
- 15 example an organic acid such as trifluoroacetic acid or an inorganic base such as lithium hydroxide optionally in an aqueous organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol, e.g. methanol at around ambient temperature. Where desired, mixtures of
- 20 such solvents may be used.

In a still further aspect of the invention a compound of formula (1) may also be prepared by functionalisation of a phenol of formula (9):

25



(9)

30

using standard substitution approaches employing for example alkylation, arylation, acylation, sulphonylation or coupling reactions. In these reactions the starting materials of formula (9) may first be obtained by use of the appropriate phenol intermediates in the reactions previously described to obtain compounds of formula (1).

Thus in one example, a phenol of formula (9) may be alkylated or arylated using a reagent R^1X^1L in which X^1 is a covalent bond or a $-(CH_2)_n$ group and L is a leaving atom or group such as a halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an

5 alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

The alkylation or arylation reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an

10 alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran at for example around 0°C to around ambient temperature. The compounds R^1X^1L are either known and readily available or may be
15 obtained by simple manipulation of known compounds, for example as described in the Examples hereinafter.

In another example, a phenol of formula (9) may be functionalised by acylation, for example by reaction with a reagent R^1X^1Hal - [wherein X^1 is

20 a $-C(O)-$, $-CH_2C(O)-$ or $-NHC(O)-$ group and Hal is a halogen atom such as a chlorine atom] in the presence of a base, such as a tertiary amine, e.g. triethylamine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride, at for example ambient temperature.

25

In a further example a compound of the invention may be obtained by sulphonylation of a phenol of formula (9) by reaction with a reagent R^1X^1L or $(Hal^1)_3CSO_2L$ [in which X^1 is $-SO_2-$ and L is a leaving group as defined above] in the presence of a base, for example an inorganic base such as

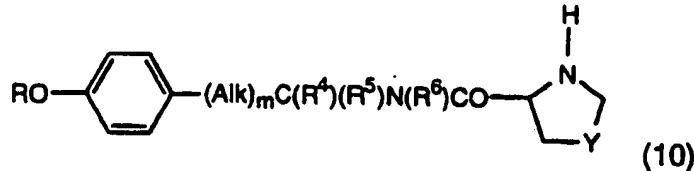
30 sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

In another example a compound of formula (1) wherein R is a group R^1X^1 [where X^1 is a covalent bond or a $-(CH_2)_n$ group] may be obtained by

35 coupling a phenol of formula (9) with a reagent R^1OH or $R^1(CH_2)_nOH$ in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g.

triphenylphosphine and an activator such as diethyl-, diisopropyl- or dimethylazodicarboxylat .

5 In a further process according to the invention a compound of formula (1) may be prepared by acylation or sulphonylation of an intermediate of formula (10):



10 Reagents for these reactions include for example compounds of the types R⁷COHal, R⁷CO₂H, R⁷SO₂Hal or R⁷NCO. The reactions may be performed using standard conditions such as those described above in relation to the acylation or sulphonylation of phenols of formula (9). It will be appreciated that in some instances and under suitable conditions the reaction may also be performed on compounds of formula (10) in which R

15 is a hydrogen atom so that acylation or sulphonylation takes place at both ends of the molecule. In general in this process any carboxyl group in intermediates of formula (10) will need to be protected, for example as a methyl ester, and, where required, the free acid subsequently regenerated by hydrolysis as described herein.

20 Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

25 Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

30 Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers

may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

- 5 In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.
- 10 The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

EDC - 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide;	
DMF - dimethylformamide;	DMSO - dimethylsulphoxide;
15 HOBT - 1-hydroxybenzotriazole;	THF - tetrahydrofuran;
TFA - trifluoroacetic acid;	NMM - N-methylmorpholine;
DCM - dichloromethane;	Ph - phenyl;
tyr - tyrosine;	Ar - aryl;
thiopro - thioproline;	pyr - pyridine;
20 Me - methyl;	Bu - butyl;
BOC - t-butoxycarbonyl.	

INTERMEDIATE 1

N-Acetyl-D-thioproline-L-tyrosine tert.butyl ester

- 25 EDC (4.22g, 22mmol) was added to a solution of N-acetyl-D-thioproline (3.50g, 20mmol), tyrosine tert.butyl ester (4.74g, 20mmol), HOBT (2.97g, 22mmol) and NMM (2.42ml, 22mmol) in DMF (80ml) at 0°. The mixture was stirred at room temperature overnight. The DMF was evaporated *in vacuo* and the residue dissolved in ethyl acetate (600ml) and water (50ml).
- 30 The organic phase was washed with 10% citric acid (150ml), saturated aqueous NaHCO₃ (150ml), water (150ml) and brine (150ml), dried (Na₂SO₄) and evaporated *in vacuo* to give the title compound as an off-white solid (7.39g, 94%); δH (DMSO-d₆, 300K) (2 rotameric species observed) 9.17 (1H, br s, ArCH), 8.43 (3, J 8.0Hz), and 8.09 (d, J 8.0Hz) together (1H, CONH), 6.98 (2H, t, J 7.6, ArH), 6.84 (2H, d, J 7.3, ArH), 4.81-4.67 (m), 4.47 (d, J 8.7Hz) and 4.35-4.21 (m), together (4H, CH_α-tyr,
- 35

$\text{CH}_\alpha\text{thiopro}$ and NCH_2S), 3.32 (dd, \downarrow 7.2, 11.6Hz), 3.17 (dd, \downarrow 7.5, 11.6Hz), 2.99-2.72 (m) together (4H, $\text{CH}_2\text{Ar} + \text{CHCH}_2\text{S}$), 2.06 (s) and 1.84 (s) together (3H, CH_3CO) and 1.36 (9H, s, CO_2^tBu); m/z (ESI, 15V) 395 ($M^+ + 1$).

5

INTERMEDIATE 2

N-Acetyl-D-thioproline-L-tyrosine methyl ester

EDC (2.11g, 11mmol) was added to a stirred solution of N-acetyl-D-thioproline (1.75g, 10mmol), tyrosine methyl ester (2.32g, 10mmol), HOBT (1.49g, 11mmol) and NMM (2.31ml, 21mmol) in DMF (50ml) at 0°. The mixture was stirred at room temperature overnight. The DMF was evaporated *in vacuo* and the residue dissolved in ethyl acetate (400ml), and water (50ml). The organic phase was washed with 10% citric acid (100ml), saturated aqueous NaHCO_3 (100ml), water (100ml) and brine (100ml), dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound as a slightly yellow powdery solid (2.75g, 78%), used without further purification. A small portion was crystallised from EtOAC to give a white microcrystalline solid, m.p. 189-190°. δH (DMSO-d_6 , 400K) 7.7 (1H, br s, CONH), 6.98 (2H, d, \downarrow 8.6Hz, ArH), 6.69 (2H, d, \downarrow 8.5Hz, ArH), 4.83 (1H, dd, \downarrow 3.9, 7.4Hz, $\text{CH}_\alpha\text{thiopro}$), 4.77 (1H, d, \downarrow 9.2 Hz, $\text{NCH}_2\text{H}_\beta\text{S}$), 4.53 (1H, dt, \downarrow 5.8, 8.1Hz, $\text{CH}_\alpha\text{tyr}$), 4.38 (1H, d, \downarrow 9.2Hz, $\text{NCH}_2\text{H}_\beta\text{S}$), 3.65 (3H, s, CO_2HC), 3.25 (1H, dd, \downarrow 7.3, 11.5Hz, $\text{CHCH}_2\text{H}_\beta\text{S}$), 3.05-2.97 (2H, m, $\text{CH}_2\text{H}_\beta\text{Ar} + \text{CHCH}_2\text{H}_\beta\text{S}$), 2.89 (1H, dd, \downarrow 8.2, 14.1Hz, $\text{CH}_2\text{H}_\beta\text{Ar}$) and 1.99 (3H, s, CH_3CO) [phenolic OH not observed at 400K, for δH (DMSO-d_6 , 300K) 9.19 (1H, br s, ArOH)]; m/z ESI, 27V), 353 ($M^+ + 1$).

INTERMEDIATE 3

3-Nitro-L-tyrosine methyl ester hydrochloride

Acetyl chloride (8.9ml, 125mmol) was added slowly to methanol (100ml) at 0°. 3-Nitro-L-tyrosine (5.65g, 25mmol) was added and the mixture refluxed for 2h. The solvent was evaporated *in vacuo* and the yellow solid obtained recrystallised from methanol to give the title compound as yellow needles (2.97g, 43%), m.p. 200-201°. (Found: C, 43.29; H, 4.69; N, 10.19. $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_5$ HCl requires C, 43.41; H, 4.74; N, 10.13%); δH (CD_3OD) 8.00 (1H, d, \downarrow 2.2Hz, ArH), 7.53 (1H, dd, \downarrow 2.3, 8.6Hz, ArH), 7.17 (1H, d, \downarrow 8.6Hz, ArH), 4.37 (1H, dd, \downarrow 6.4, 7.0Hz, CH_α), 3.83 (3H, s,

CO_2CH_3), 3.29 (1H, dd, \downarrow 6.3, 14.6 Hz, $\text{CH}_A\text{H}_B\text{Ar}$) and 3.20 (1H, dd, \downarrow 7.1, 14.6 Hz, $\text{CH}_A\text{H}_B\text{Ar}$); m/z (ES, 27V) 241 ($M^+ + 1$).

INTERMEDIATE 4

5 **N-Acetyl-D-thioproline-3-nitro-L-tyrosine methyl ester**

EDC.HCl (1.056g, 5.5mmol) was added to a solution of *N*-acetyl-*D*-thioproline (875mg, 5mmol), Intermediate 3 (1.38g, 5mmol), HOBT (743mg, 5.5mmol) and NMM (1.15ml, 10.5mmol) in DMF (25ml) at room temperature. The reaction mixture was stirred overnight. The DMF was evaporated *in vacuo* and the residue dissolved in ethyl acetate (150ml) and water (50ml). The organic phase was washed with hydrochloric acid (1M, 30ml), saturated aqueous NaHCO_3 (30ml), water (50ml) and brine (30ml), dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound as a yellow foam (1.59g, 80%); δ H (DMSO-d₆, 300K) (2 rotameric species observed) 10.79 (s) and 10.76 (s) together (1H, ArOH), 8.61 (d, \downarrow 8.2Hz) and 8.32 (d, \downarrow 8.3Hz) together (1H, CONH), 7.75-7.71 (1H, m, ArH), 7.44-7.37 (1H, m, ArH), 7.06-7.01 (1H, m, ArH), 4.74-4.67 (m) and 4.56-4.43 (m) and 4.44 (d, \downarrow 8.6Hz), and 4.19 (d, \downarrow 9.7Hz) together (4H, 2x CH_α + NCH_2S), 3.64 (3H, s, CO_2CH_3), 3.33-2.77 (4H, m, $\text{CHCH}_2\text{S} + \text{CH}_2\text{Ar}$) and 2.03 (s) and 1.84 (s) together (3H, CH_3CO); m/z (ES, 30V) 398 ($M^+ + 1$).

INTERMEDIATE 5

α -Methyl-L-tyrosine methyl ester hydrochloride

Anhydrous hydrogen chloride was bubbled through a solution of α -methyl-*L*-tyrosine (1g, 5.13mmol) in methanol (100ml) for a few minutes and the solution stirred at room temeprature for 48h. The solvent was evaporated *in vacuo* and the residue freeze dried from a mixture of methanol and water to give the title compound as a white powder (1.28g, 100%); δ H (CD₃OD) 7.00 (2H, d, \downarrow 8.6Hz, ArH), 6.78 (2H, d, \downarrow 8.6Hz, ArH), 3.82 (3H, s, CO_2CH_3), 3.19 (1H, d, \downarrow 14.3Hz, $\text{CH}_A\text{H}_B\text{Ar}$), 3.01 (1H, d, \downarrow 14.3Hz, $\text{CH}_A\text{H}_B\text{Ar}$) and 1.59 (3H, s, CCH₃); m/z (ES, 27V) 210 ($M^+ + 1$).

INTERMEDIATE 6

***N*-Acetyl-D-thioproline- α -methyl-L-tyrosine methyl ester**

35 EDC.HCl (760mg, 3.96mmol) was added to a solution of *N*-acetyl-*D*-thioproline (630mg, 3.6mmol), Intermediate 5 (880mg, 3.6mmol), HOBT

(535mg, 3.96mmol) and NMM (834 μ l, 7.6mmol) in DMF (20ml). The mixtur was stirred at room temperature overnight. The DMF was evaporated *in vacuo* and th residue dissolv d in ethyl acetate (150ml) and ater (50ml). The organic phase was washed with 10% citric acid

5 (50ml), saturated aqueous NaHCO₃ (50ml) and water (50ml), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by column chromatography (SiO₂, methanol/DCM, 7:93) to give the title compound as a colourless gum (680mg, 52%); δ H (DMSO-d₆, 400K) 7.40 (1H, br s, CONH), 6.93 (2H, d, \downarrow 8.6Hz, ArH), 6.68 (2H, d, \downarrow 8.3Hz, ArH), 4.84 (1H, dd, \downarrow 3.8, 7.4Hz, CH₂thiopro), 4.78 (1H, d, \downarrow 9.2Hz, NCH₂HBS), 4.40 (1H, d, \downarrow 9.2Hz, NCH₂HBS), 3.63 (3H, s, CO₂CH₃), 3.30 (1H, dd, \downarrow 7.4, 11.5Hz, CHCH₂HBS), 3.16 (1H, dd, \downarrow 3.8, 11.5Hz, CHCH₂HBS), 3.13 (1H, d, \downarrow 13.7Hz, CH₂H₂Ar), 3.03 (1H, d, \downarrow 13.7Hz, CH₂H₂Ar), 2.02 (3H, s, CH₃CO) and 1.38 (3H, s, CCH₃); m/z (ES, 15V) 367 (M⁺ + 1).

15

INTERMEDIATE 7

2,4,6-Trichlorobenzyl alcohol

A solution of lithium aluminium hydride (1M in THF, 18mmol, 18ml) was added slowly to a solution of 2,4,6-trichlorobenzoyl chloride (4.35g,

20 17.8mmol) in THF (70ml) at 0°. After 1h water (685 μ l) was added, followed by aqueous sodium hydroxide (3M, 685 μ l) and more water (2.06ml). The suspension was stirred vigorously for 1h, the precipitate filtered off and the filtrate evaporated *in vacuo* to give a slightly yellow solid. Recrystallisation from diisopropylether gave the title compound as
25 white needles (2.63g, 70%), m.p. 100-101°. δ H (CDCl₃) 7.35 (2H, s, ArH), 4.91 (2H, br s, CH₂CH) and 2.07 (1H, br s, CH); m/z (ES, 60V) 193 (M-OH).

INTERMEDIATE 8

2,4,6-Trichlorobenzyl bromide

Thionyl bromide (682 μ l, 8.8mmol) was added to a solution of Intermediate 7 (846mg, 4mmol) in DCM (20ml) at 0°. The reaction was stirred at room temperature overnight then quenched with water. The mixture was diluted with DCM (100ml), washed with saturated aqueous NaHCO₃ (30ml) and

35 water (30ml), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purifi d by column chromatography (short plug SiO₂, hexane) to giv the

title compound as a colourless oil which crystallised on standing to white crystals (982mg, 89%), m.p. 51-52°. δH (CDCl₃) 7.36 (2H, s, ArH) and 4.70 (2H, s, CH₂Br).

5 **INTERMEDIATE 9**

N-Boc-D-thioproline-(O-benzyl)-L-tyrosine methyl ester

NMM (1.73g, 1.9ml, 17.13mmol), HOBT (2.53g, 18.74mmol) N-Boc-D-thioproline (4.0g, 17.17mmol) and EDC (3.30g, 17.19mmol) were added sequentially to a stirred solution of O-benzyl-L-tyrosine methyl ester hydrochloride (5.02g, 15.59mmol) in dry DMF (50ml). The reaction mixture was stirred at room temperature under N₂ for 3h. The DMF was removed *in vacuo* and the residue partitioned between EtOAc (150ml) and 5% aqueous Na₂CO₃ (50ml). The phases were separated and the aqueous phase re-extracted with EtOAc (2 x 50ml). The combined organic extracts were washed consecutively with 5% aqueous hydrochloric acid (30ml), 5% aqueous Na₂CO₃ (30ml) and brine (20ml) then dried (Na₂SO₄) and evaporated *in vacuo* to afford the title compound as a straw coloured oil (7.8g). This was used without further purification but can be purified by flash chromatography (SiO₂; 2% MeOH/DCM). δH (DMSO-d₆), 7.48-7.28 (5H, m, PhH), 7.03 (2H, d, J 8.6Hz, ArH), 6.88 (2H, d, J 8.6Hz, ArH), 6.82 (1H, br s NHCO), 5.02 (2H, s, PhCH₂O), 4.81 (1H, apparent, dt, J 5.8Hz, CH_α-tyr), 4.64 (1H, br d J ~9Hz, NCH₂BS), 4.25 (1H, d, J 9.2Hz, NCH₂BS), 3.69 (3H, s, CO₂CH₃), 3.34 (1H, br d, J 11Hz, CHCH₂BS), 3.13 (1H, br d J ~7, ~11Hz, CHCH₂BS) 3.06 (1H, d, J 5.8Hz, CH₂Ar) and 1.45 (9H, s CO₂tBu); m/z (ESI, 15V) 523 (MNa⁺, 55), 501 (MH⁺, 74, 445 (100).

INTERMEDIATE 10

D-Thioproline-(O-benzyl)-L-tyrosine methyl ester

30 Intermediate 9 (8.2g) was stirred in trifluoroacetic acid (50ml) and DCM (50ml) at room temperature for 1h. The solvent was removed *in vacuo* and the residue partitioned between EtOAc (150ml) and saturated aqueous NaHCO₃ (50ml). The phases were separated and the aqueous phase re-extracted with EtOAc (32 x 50ml). The combined organic extracts were washed with brine (30ml), dried (Na₂SO₄) and evaporated *in*

vacuo. The obtained solid was treated with diethyl ether (50ml) and filtered off with a little ether washing affording the title compound as white needles (5.3g, 8.1%): m.p. 138-140°. (Found C, 62.88; H, 6.06; N, 6.92. C₂₁H₂₄N₂O₄S requires C, 62.98; H, 6.04; N, 7.00%); δH (50 %

5 CDCl₃/CD₃OD) 7.42-7.23 (5H, m, PhH), 7.03 (2H, d, J 8Hz, ArH), 6.86 (2H, d, J 8.7Hz, ArH), 5.02 (2H, s, OCH₂Ph), 4.68 (1H, dd, J 7.5, 5.5Hz, CHα-tyr), 4.10 (1H, d, J 9.6Hz, NCH₂HS), 3.96 (1H, d, J 9.6Hz, NCH₂HS), 3.96-3.94 (1H, m, CHα-thiopro), 3.69 (3H, s, CO₂CH₃), 3.13-3.04 (2H, m) and 3.01-2.92 (2H, m) together (4H, CHCH₂S and CH₂Ar).
 10 m/z (ESI, 27V) 401 (MH⁺, 100).

EXAMPLE 1

N-Acetyl-D-thioproline-(O-2,6-dichlorobenzoyl)-L-tyrosine tert.butyl ester

15 A solution of Intermediate 1 (705mg, 1.79mmol) in THF (5ml) was added to a suspension of sodium hydride (60% in oil, 79mg, 1.97mmol) and 2,6-dichlorobenzoyl chloride (283μl, 1.97mmol) in THF (10ml) at 0°. The mixture was stirred at room temperature for 6h then quenched with aqueous NH₄Cl (5ml). The mixture was extracted with DCM (2 x 75ml)
 20 and the combined organic extracts dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by chromatography (SiO₂; ethyl acetate/hexane 80:20) to give the title compound as a white foam (920mg, 91%); δH (DMSO-d₆, 300K) (2 rotameric species observed) 8.55 (d, J 7.9Hz), and 8.25 (d, J 8.0Hz), together (1H, NHCO), 7.70-7.59 (3H, m, COArH), 7.38-7.34 (2H, m, CH₂ArH), 7.21-7.17 (2H, m, CHArH), 4.80-4.67 (m) and 4.50-4.34 (m) and 4.48 (d, J 8.7Hz) and 4.23 (d, J 9.6Hz) together (4H, 2 x CHα + NCH₂S), 3.30-2.80 (4H, m, CH₂Ar + CHCH₂S), 2.07 (s) and 1.83 (s) together (3H, CH₃CO) and 1.38 (9H, s, CO₂tBu); m/z (ESI, 15V) 567 (M⁺ + 1).

30

EXAMPLE 2

N-Acetyl-D-thioproline-(O-2,6-dichlorobenzoyl)-L-tyrosine

A solution of the compound of Example 1 (910mg, 1.60mmol) in a mixture

of TFA/H₂O (9:1, 20ml) was stirred at room temperature for 2h.

35 The solvents were evaporated *in vacuo* and the residue freeze dried from a mixture of methanol/H₂O to give the title compound as a fluffy white solid

(809mg, 99%) δH (DMSO-d₆, 400K) 7.75 (1H, br d, CONH), 7.62-7.53 (3H, m, COArH), 7.34 (2H, d, J 8.7Hz, CH₂-ArH), 7.20 (2H, d, J 8.7Hz, CH₂ArH), 4.82 (1H, dd, J 3.9, 7.3Hz, CH₂thiopro), 4.76 (1H, d, J 9.2Hz CH₂H₂S), 4.57 (1H, dt, J 5.4, 8.4Hz, CH₂tyr), 4.37 (1H, d, J 9.1Hz, NCH₂H₂S), 3.25 (1H, dd, J 7.4, 11.6Hz, CHCH₂H₂S), 3.19 (1H, dd, J 5.3, 14.1Hz, CH₂A₂H₂Ar), 4.07-2.99 (2H, m, CHCH₂H₂S + CH₂A₂H₂Ar) and 1.98 (3H, s, CH₃CO); m/z (ESI, 27V) 511 M⁺ + 1; [α]_D^{24.5} = + 76.53° (c, = 0.69, methanol).

10 **EXAMPLE 3**

N-Acetyl-D-thioproline-(O-2,6-dimethoxybenzoyl)-L-tyrosine methyl ester

A solution of Intermediate 2 (352mg, 1mmol) in DMF (5ml) was added to a suspension of sodium hydride (60% in oil, 44mg, 1.1mmol) in DMF (3ml) at 15 0°. After 5 min at room temperature a yellow solution was obtained, to this was added a solution of 2,6-dimethoxybenzoyl chloride (241mg, 1.22mmol) in DMF (2ml). The mixture was stirred for 1h then quenched with water and the DMF evaporated *in vacuo*. The residue was dissolved in ethyl acetate (100ml) and washed in water (3 x 30ml) and brine (30 ml), 20 dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by chromatography (SiO₂, DCM/methanol, 95:5) to give the title compound as a yellow gum (462mg, 90%); δH (DMSO-d₆, 300K) (2 rotameric species observed) 8.63 (3, J 8.2Hz) and 8.38 (d, J 8.1Hz) together (1H, CONH), 7.43 (1H, t, J 8.4Hz, CO-ArH), 7.29 (2H, t, J 8.1Hz), CH₂ArH, 7.09-7.06 (2H, m, CH₂ArH), 6.77 (2H, d, J 8.4Hz, CO-ArmH), 4.79-4.68 (m) and 4.60-4.44 (m) and 4.45 (d, J 8.7Hz) and 4.23 (d, J 9.7Hz) together (4H, 2 x CH₂ + NCH₂S), 3.84 (6H, s, 2 x ArOMe), 3.65 (s) and 3.64 (s) together (3H, CO₂Me), 3.32-2.73 (4H, m, CH₂Ar + CHCH₂S) and 2.06 (s) and 1.84 (s) together (3H, CH₃CO); m/z (ESI, 15V) 517 (M⁺ + 1).

25 30 **EXAMPLE 4**

N-Acetyl-D-thioproline-(O-2,6-dimethoxybenzoyl)-L-tyrosine

Lithium hydroxide (41mg, 0.97mmol) was added to a solution of the compound of Example 3 (455mg, 0.88mmol) in a mixture of THF (10ml) 35 and water (10ml). The mixture was stirred at room temperature for 10 min then the THF was evaporated *in vacuo*. The residue was purified by

chromatography (SiO_2 ; DCM/methanol/acetic acid, 90:5:5). The gum obtained was freeze-dried from a mixture of methanol and water to give the title compound as a fluffy white solid (401mg, 91%). δH (DMSO- d_6 , 400K) 7.7 (1H, br d, CONH), 7.40 (1H, t, \downarrow 8.4Hz, COAr H), 7.28 (2H, d, \downarrow

- 5 8.7Hz, CH_2ArH), 7.09 (2H, d, \downarrow 8.6Hz, CH_2ArH), 6.77 (2H, d, \downarrow 7.8Hz, COAr $_m\text{H}$), 4.83 (1H, dd, \downarrow 4.0, 7.3 Hz, CH α thiopro), 4.77 (1H, d, \downarrow 9.2Hz, NCH $\alpha\text{H}_2\text{S}$), 4.57-4.51 (1H, m, CH α tyr), 4.38 (1H, d, \downarrow 98.2Hz, NCH $\alpha\text{H}_2\text{S}$), 3.87 (6H, s, 2 x COArOMe), 3.25 (1H, dd, \downarrow 7.4, 11.5Hz, CHCH $\alpha\text{H}_2\text{S}$), 3.17 (1H, dd, \downarrow 5.4, 14.1 $\text{CH}_2\text{ArH}_2\text{Ar}$), 3.06-2.98 (2H, m, CHCH $\alpha\text{H}_2\text{S}$ + 10 CH $\alpha\text{H}_2\text{Ar}$) and 1.99 (3H, s, CH_3CO), m/z (ESI, 15V) 503 ($M^+ + 1$).

EXAMPLE 5

N-Acetyl-D-thioproline-(Q-benzyl)-L-tyrosine methyl ester

- EDC (211mg, 1.1mmol) was added to a stirred solution of N-acetyl-D-thioproline (175mg, 1mmol), Q-benzyl tyrosine methyl ester hydrochloride (322mg, 1mmol), HOBT (149mg, 1.1mmol) and NMM (242 μ l, 2.2mmol) in DCM (10ml) at 0°. The mixture was stirred at room temperature overnight then diluted with DCM (100ml). The DCM solution was washed with 1M hydrochloric acid (30ml), saturated aqueous NaHCO₃ (30ml) and water (30ml), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by chromatography (SiO_2 ; ethyl acetate) to give the title compound as a white foam (417mg, 94%); δH (DMSO- d_6 , 300K) (2 rotameric species observed) 8.55 (d, \downarrow 7.8Hz) and 8.28 (3, \downarrow 8.1Hz) together (1H, NHCO), 7.43-7.25 (5H, m, Ph), 7.14-7.08 (2H, m, ArH), 6.92-6.88 (2H, m, ArH), 5.06 (2H, s, CH_2Ph), 4.79-4.66 (m) and 4.45-4.42 (m) and 4.21 (d, \downarrow 9.7Hz) together (4H, CH α -tyr, CH α -thiopro and NCH₂S), 3.62 (s) and 3.61 (s) together (3H, CO₂Me), 3.28-2.71 (4H, m, CHCH₂Ar + CHCH₂S) and 2.04 (s) and 1.82 (s) together (3H, CH_3CO); m/z (ESI, 15V) 443 ($M^+ + 1$).
- 30 The following compounds were prepared in a similar manner using the appropriate tyrosine esters:

N-Acetyl-D-thioproline-(Q-benzyl)-L-tyrosine tert.butyl ester

- δH (DMSO- d_6 400K), 7.64 (1H, br d, CONH), 7.43-7.30 (5H, m, Ph), 7.12 (2H, d, \downarrow 8.8Hz, ArH), 6.92 (2H, d, \downarrow 8.7Hz, ArH), 5.09 (2H, s, OCH₂Ph), 4.82 (1H, dd, \downarrow 7.3, 3.8Hz, CH α thiopro), 4.77 (1H, d, \downarrow 9.2Hz, NCH $\alpha\text{H}_2\text{S}$),

4.43 (1H, dt, \downarrow 8.1, 6.0Hz, CH α tyr), 4.37 (1H, d, \downarrow 9.2Hz, NCH_AH_BS), 3.25 (1H, dd, \downarrow 11.5; 7.4Hz, CHCH_AH_BS), 3.03 (1H, dd, \downarrow 11.5, 3.8Hz, CHCH_AH_BS), 3.02 (1H, dd, \downarrow 14.2, 6.2Hz, CHCH_AH_BAr), 2.91 (1H, dd, \downarrow 14.2, 8.1Hz, CHCH_AH_BAr), 1.99 (3H, s, COCH₃) and 1.40 (9H, s, CO₂tBu) 5 (acid proton not observed at 400K); m/z (ESI, 15V) 485 ($M^+ + 1$).

N-Acetyl-D-thioproline-(O-benzyl)-L-tyrosine ethyl ester

δH (DMSO-d₆ 390K), 7.73(1H, br s, NH), 7.44-7.30 (5H, m, Ph-H), 7.12 (2H, ABd, \downarrow 8.7Hz, Ar-H), 6.92 (2H, m, Ar-H), 5.09 (2H, s, CH₂OAr), 4.79 (2H, m, CH α thiopro + NCH_AH_BS), 4.53 (1H, m, CH α tyr), 4.36 (1H, m, NCH_AH_BS), 4.10 (2H, q, \downarrow 7.1Hz, CH₂CH₃), 3.31-2.88 (4H, m, CHCH₂S + CHCH₂Ar), 1.98 (s) and 1.95 (s) together (3H, MeCO) and 1.18 (3H, t, \downarrow 7.1Hz, CH₂CH₃); 10 m/z (ESI, 60V) 457 ($M^+ + 1$).

15 **EXAMPLE 6**

N-Acetyl-D-thioproline-(O-benzyl)-L-tyrosine

Lithium hydroxide (47mg, 1.1mmol) was added to a solution of the compound of Example 5 (410mg, 0.93mmol) in a mixture of THF (10ml) and water 10ml). The mixture was stirred for 30min at room temperature 20 then the THF was evaporated *in vacuo*. The aqueous residue was acidified (1M hydrochloric acid and extracted with DCM (2 x 50ml)). The combined organic extracts were dried (Na₂SO₄) and evaporated *in vacuo* to give a gummy solid. This was dissolved in methanol, diluted with water and freeze-dried to give the title compound as a fluffy white solid (369mg, 25 93%). δH (DMSO-d₆, 400K) 7.65 (1H, br d, CONH), 7.43-7.29 (5H, m, Ph), 7.12 (2H, d, \downarrow 8.5Hz, ArH), 6.91 (2H, d, \downarrow 8.6, ArH), 5.08 (2H, s, CH₂Ph), 4.81 (1H, dd, \downarrow 3.9-7.4Hz, CH α -thiopro), 4.76 (1H, d, \downarrow 9.2Hz, NCH_AH_BS), 4.50 (1H, dt, \downarrow 5.4, 8.3Hz, CH α tyr), 4.36 (1H, d, \downarrow 9.1Hz, NCH_AH_BS), 3.23 (1H, dd, \downarrow 7.1, 11.5Hz, CHCH_AH_BS), 3.07 (1H, dd, \downarrow 5.4, 30 14.1 Hz, CH_AH_BAr), 2.99 (1H, dd, \downarrow 3.9, 11.5Hz, CHCH_AH_BS), 2.91 (1H, dd, \downarrow 8.4, 14.2Hz, CH_AH_BAr) and 1.97 (3H, s, CH₃CO) [COOH not observed at 400K. δH (DMSO-d₆, 300K) 12.7 1Hv. br s. CO₂H]; m/z (ESI, 15V) 429 ($M^+ + 1$).

35 **EXAMPLE 7**

N-Acetyl-D-thioproline-(O-2,6-dichlorobenzyl)-L-tyrosine methyl ester

A solution of Intermediate 2 (352mg, 1mmol) in DMF (5ml) was added to a suspension of sodium hydride (60% in mineral oil, 44mg, 1.1mmol) in DMF

5 (3ml) at room temperature. After 5min a solution of 2,6 dichlorobenzyl bromide (288mg, 1.2mmol) in DMF (2ml) was added and the mixture stirred for 90min. The reaction was quenched with a few drops of water and the DMF was removed *in vacuo*. The residue was dissolved in ethyl acetate (100ml), washed with water (2 x 50ml) and brine (25ml), dried 10 (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by column chromatography (SiO_2 ; methanol/DCM 5:95) to give the title compound as a white foam (499mg, 97%); δH (DMSO-d_6 , 300K) (2 rotameric species observed) 8.57 (d, \downarrow 8.2Hz) and 8.31 (d, \downarrow 8.1Hz), together (1H, NHCO), 7.57-7.43 (3H, m, OCH_2ArH), 7.18-7.12 (2H, t, \downarrow 8.1Hz, CHCH_2ArH), 6.98-15 6.94 (2H, m, CHCH_2ArH), 5.19 (2H, s, OCH_2Ar), 4.79-4.68 (m) and 4.50-4.44 (m) and 4.45 (d, \downarrow 8.8Hz), and 4.23 (d, \downarrow 9.7Hz) together (4H, 2 x $\text{CH}_\alpha + \text{NCH}_2\text{S}$), 3.64 (s) and 3.635 (s) together (3H, CO_2CH_3), 3.35-3.27 (m) and 3.17-2.49 (m) together (4H, $\text{CHCH}_2\text{Ar} + \text{CHCH}_2\text{S}$) and 2.05 (s) and 1.83 (s) together (3H, CH_3CON); m/z (ESI, 15V) 511 (M^{++1}).

20

The following compound was prepared in a similar manner:

N-Acetyl-D-thioproline-(O-2,6-dichlorobenzyl)-L-tyrosine ethyl ester

δH (DMSO-d^6 , 390K) 7.51 (1H., br d, \downarrow 2.0Hz, NH), 7.48-7.41 (3H, m, Cl_2 -

25 Ar-H), 7.14 (2H, d, \downarrow 8.6Hz, Ar-H), 6.96 (2H, d, \downarrow 8.6Hz, Ar-H), 5.26 (2H, s, CH_2OAr), 4.81 (1H, m, CH_α -thiopro), 4.76 (1H, d, \downarrow 9.2Hz, NCH_2HS), 4.53 (1H, m, CH_α tyr), 4.38 (1H, d, \downarrow 9.2Hz, NCH_2HS), 4.11 (2H, q, \downarrow 7.1Hz, CH_2CH_3), 3.24-2.99 (4H, m, $\text{CHCH}_2\text{S} + \text{CHCH}_2\text{Ar}$), 1.99 (3H, s, COMe) and 1.19 (3H, t, \downarrow 7.1Hz, CH_2CH_3). m/z (ESI, 60V), 527, 525 (M^{++1}).

30 1.

EXAMPLE 8

N-Acetyl-D-thioproline-(O-2,6-dichlorobenzyl)-L-tyrosine

Lithium hydroxide (44mg, 1.05mmol) was added to a solution of the

35 compound of Example 7 (490mg, 0.959mmol) in a mixture of THF (10ml) and water (10ml). The mixture was stirred at room temperature for 15min

then the THF was evaporated *in vacuo*. The aqueous residue was acidified (1M hydrochloric acid) and extracted with DCM (2x50ml). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound as a white solid (464mg, 97%) (Found: C, 53.02; H, 4.46; N, 5.50. $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_5\text{SCl}_2$ requires C, 53.12; H, 4.46; N, 5.63%); δH (DMSO-d₆, 400K) 7.63 (1H, brd, CONH), 7.51-7.38 (3H, m, OCH₂ArH), 7.16 (2H, d, \downarrow 8.7Hz, CHCH₂ArH), 6.95 (2H, d, \downarrow 8.7Hz, CHCH₂ArH), 5.26 (2H, s, OCH₂Ar), 4.83 (1H, dd, 3.9, 7.4, CH_α thiopro), 4.77 (1H, d, \downarrow 9.2Hz, NCHAHBS), 4.53 (1H, dt, \downarrow 5.4, 8.3Hz, CH α tyr), 4.37 (1H, d, \downarrow 9.2Hz,

5 NCHAH_B S), 3.24 (1H, dd, \downarrow 7.3, 11.5Hz, CHCHAHBS), 3.10 (1H, dd, \downarrow 5.4, 14.1Hz, CHCHAH_BAr), 3.00 (1H, dd, \downarrow 3.9, 11.5 Hz, CHCHAHBS), 2.94 (1H, dd \downarrow 8.4, 14.1 Hz, CHCHAH_BAr) and 1.99 (3H, s, CH_3CO); m/z (ESI, 27V) 497 ($\text{M}^+ + 1$).

10 15 **EXAMPLE 9**

N-Acetyl-D-thioproline-(O-2,6-dichlorobenzyl)-3-nitro-L-tyrosine methyl ester

A solution of Intermediate 4 (596mg, 1.5mmol) in DMF (5ml) was added to a suspension of sodium hydride (60% in mineral oil, 66mg, 1.65mmol) in 20 DMF (10ml) at 0°. After 10min a solution of 2,6-dichlorobenzyl bromide (432mg, 1.8mmol) in DMF (3ml) was added and the mixture stirred at 0° for 2h and at room temperature for 1h. The reaction was quenched with a few drops of water and the DMF removed *in vacuo*. The residue was dissolved in ethyl acetate (100ml), washed with water (2x30ml) and brine (30ml), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by column chromatography (SiO_2 ;methanol/DCM 5:95) to give the title compound as a yellow oil (600mg, 72%); δH (DMSO-d₆, 300K) (2 rotameric species observed) 8.63 (d, \downarrow 8.0Hz) and 8.37 (d, \downarrow 8.3Hz) together (1H, CONH), 7.75-7.71 (1H, m, CHCH₂ArH), 7.58-7.45 (5H, m, ArH), 5.38 (2H, s, OCH₂Ar), 4.75-4.68 (m) and 4.56-4.48 (m) and 4.44 (d, \downarrow 8.6Hz) and 4.20 (d, \downarrow 9.7Hz) together (4H, 2x CH_α + NCH₂S), 3.66 (3H, s, CO_2CH_3), 3.29-2.73 (4H, m, CHCH₂Ar + CHCH₂S) and 2.04 (s) and 1.85 (s) together (3H, CH_3CO); m/z (ES, 15V) 556 ($\text{M}^+ + 1$).

25 30 35 **EXAMPLE 10**

N-Acetyl-D-thioproline-(O-2,6-dichlorobenzyl)-3-nitro-L-tyrosine

Lithium hydroxide (49mg, 1.17mmol) was added to a solution of the compound of Example 9 (590mg, 1.06mmol) in a mixture of THF (10ml) and water (10ml). The mixture was stirred at room temperature for 30min then the THF was evaporated *in vacuo*. The aqueous residue was

- 5 acidified (1M, hydrochloric acid) and extracted with ethyl acetate (2x75ml). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was freeze dried from a mixture of methanol and water to give the title compound as a fluffy yellow solid (510mg, 89%) (Found: C, 48.39; H, 3.91; N, 7.60. $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_7\text{SCl}_2$ requires C, 48.72; H, 3.90; N, 7.75%); δH (DMSO-d_6 , 400K) 7.85 (1H, br d, CONH), 7.67 (1H, d, \downarrow 2.2Hz, ArH), 7.54-7.41 (5H, m, ArH), 5.44 (2H, s, OCH_2Ar), 4.82 (1H, dd, \downarrow 4.0, 7.3Hz, $\text{CH}_\alpha\text{thiopro}$), 4.76 (1H, d, \downarrow 9.1Hz, $\text{NCH}_\alpha\text{H}_\beta\text{S}$), 4.57 (1H, dt, \downarrow 5.2, 8.7Hz, $\text{CH}_\alpha\text{tyr}$), 4.37 (1H, d, \downarrow 9.2Hz, $\text{NCH}_\alpha\text{H}_\beta\text{S}$), 3.28-3.16 (2H, m, $\text{CHCH}_\alpha\text{H}_\beta\text{Ar} + \text{CHCH}_\alpha\text{ACH}_\beta\text{S}$), 3.06-2.98 (2H, m, $\text{CHCH}_\alpha\text{H}_\beta\text{Ar} + \text{CHCH}_\alpha\text{H}_\beta\text{S}$) and 1.99 (3H, s, CH_3CO); m/z (ES, 30V) 542 ($M^+ + 1$).

EXAMPLE 11

N-Acetyl-D-thioproline- α -methyl-(O-2,6-dichlorobenzoyl)-L-tyrosine methyl ester

- 20 A solution of Intermediate 6 (347mg, 0.948mmol) in DMF (5ml) was added to a suspension of sodium hydride (60% in mineral oil, 40mg, 0.995mmol) in DMF (5ml) at room temperature. After 10min 2,6-dichlorobenzoyl chloride (150 μl , 1.04mmol) was added and the mixture stirred for 1h. The reaction was quenched with a few drops of water and the DMF was
- 25 evaporated *in vacuo*. The residue was dissolved in ethyl acetate (10ml), washed with water (2x30ml) and brine (30ml), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by column chromatography (SiO_2 , methanol/DCM 5:95) to give the title compound as a yellow gum (423mg, 83%); δH (DMSO-d_6 , 400K) 7.63-7.46 (4H, m, CONH + COArH),
- 30 7.30 (2H, d, \downarrow 8.8Hz, ArH), 7.21 (2H, d, \downarrow 8.7Hz, ArH), 4.86 (1H, dd, \downarrow 3.89, 7.4Hz, $\text{CH}_\alpha\text{thiopro}$), 4.78 (1H, d, \downarrow 9.1Hz, $\text{NCH}_\alpha\text{H}_\beta\text{S}$), 4.44 (1H, d, \downarrow 9.1Hz, $\text{NCH}_\alpha\text{H}_\beta\text{S}$), 3.66 (3H, s, CO_2CH_3), 3.38-3.14 (4H, m, $\text{CHCH}_2\text{S} + \text{CH}_2\text{Ar}$), 2.05 (3H, s, CH_3CO) and 1.40 (3H, s, CCH_3); m/z (ES, 15V) 539 ($M^+ + 1$).

35

EXAMPLE 12

N-Acetyl-D-thioproline- α -methyl-(O-2,6-dichlorobenzoyl)-L-tyrosine

Lithium hydroxide (34mg, 0.82mmol) was added to a solution of the compound of Example 11 in a mixture of THF (7ml) and water (7ml). The mixture was stirred at room temperature for 7h and the THF was

5 evaporated *in vacuo*. The aqueous residue was acidified (1M, hydrochloric acid) and extracted with DCM (2x75ml). The extracts were dried (Na_2SO_4) and evaporated *in vacuo*. Purification by column chromatography (SiO_2 , methanol / acetic acid / DCM, 5:5:90) and freeze drying from a mixture of methanol and water gave the title compound as a
 10 fluffy white solid (275mg, 64%). (Found: C, 51.81; H, 4.18; N, 5.13. $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_6\text{SCl}_2$, $(\text{H}_2\text{O})_{0.4}$ requires C, 51.87; H, 4.32; N, 5.26%); δH (DMSO- d_6 , 400K) 7.63-7.54 (3H, m, COArH), 7.43 (1H, br s, CONH), 7.31 (2H, d, \downarrow 8.7Hz, ArH), 7.19 (2H, d, \downarrow 8.7Hz, ArH), 4.86 (1H, dd, \downarrow 3.9, 7.4Hz, CHthiopro), 4.79 (1H, d, \downarrow 9.2Hz, NCH_2HBS), 4.42 (1H, d, \downarrow 9.2Hz, NCH_2HBS), 3.38-3.26 (3H, m, $\text{CH}_2\text{H}_2\text{Ar} + \text{CHCH}_2\text{H}_2\text{S}$), 3.17 (1H, dd, \downarrow 3.9, 11.5Hz, $\text{CHCH}_2\text{H}_2\text{S}$), 2.02 (3H, s, CH_3CO) and 1.45 (3H, s, CCH_3); m/z (ES, 15V) 525 ($M^+ + 1$).

EXAMPLE 13

20 **N-Acetyl-D-thiaproline-(O-2,4,6-trichlorobenzyl)-L-tyrosine methyl ester**

A solution of Intermediate 2 (528mg, 1.5mmol) in DMF (5ml) was added to a suspension of sodium hydride (60% in mineral oil, 66mg, 1.65mmol) in DMF (5ml) at 0°. After 10 min a solution of Intermediate 8 (453mg, 1.65mmol) in DMF (5ml) was added and the mixture stirred at 0° for 2h.

25 The reaction was quenched with a few drops of water and the DMF was removed *in vacuo*. The residue was dissolved in ethyl acetate (150ml), washed with water (2x50ml) and brine (25ml), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by column chromatography (SiO₂, ethyl acetate/hexane, 90/10) to give the title compound as a colourless viscous oil (619mg, 76%); δH (DMSO- d_6 , 300K) (2 rotameric species observed) 8.57 (d, \downarrow 8.2Hz) and 8.31 (d, \downarrow 8.2Hz) together (1H, CONH), 7.77 (2H, s, OCH_2ArH), 7.15 (2H, t, \downarrow 8.0Hz, CHCH_2ArH), 6.97-6.93 (2H, m, CHCH_2ArH), 5.15 (2H, s, OCH_2Ar), 4.79-4.67 (m) and 4.50-4.43 (m) and 4.46 (d, \downarrow 8.7Hz) and 4.22 (d, \downarrow 9.7Hz) together (4H, 2x CH_α

+ NCH₂S), 3.63 (s) and 3.64 (s) tog ther (3H, CO₂CH₃), 3.31-2.69 (4H, m, CHCH₂Ar + CHCH₂S) and 2.05 (s) and 1.83 (s) together (3H, CH₃CO); m/z (ES, 60V) 545 ($M^+ + 1$).

5 **EXAMPLE 14**

N-Acetyl-D-thioproline-(O-2,4,6-trichlorobenzyl)-L-tyrosine

Lithium hydroxide (52mg, 1.23mmol) was added to a solution of the compound of Example 13 (610mg, 1.12mmol) in a mixture of THF (11ml) and water (11ml). The mixture was stirred at room temperature for 30min and the THF removed *in vacuo*. The aqueous residue was acidified (1M hydrochloric acid) and extracted with DCM (2x50ml). The combined extracts were dried (Na₂SO₄) and evaporated *in vacuo*. The residue was freeze dried from a mixture of methanol and water to give the title compound as a fluffy white solid (538mg, 90%). (Found: C, 49.17; H, 3.99; N, 5.18. C₂₂H₂₁N₂O₅SCl₃. 0.25 (H₂O) requires C, 49.27; H, 4.04; N, 5.22%); δH (DMSO-d₆, 400K) 7.65 (1H, br d, CONH), 7.61 (2H, s, OCH₂ArH), 7.16 (2H, d, J 8.7Hz, CHCH₂ArH), 6.95 (2H, d, J 8.7Hz, CHCH₂ArH), 5.23 (2H, s, OCH₂Ar), 4.82 (1H, dd, J 3.9, 7.4Hz, CH_αthiopro), 4.77 (1H, d, J 9.2Hz, NCHAHB_S), 4.52 (1H, dt, J 5.4, 8.3Hz, CH_αtyr), 4.37 (1H, d, J 9.2Hz, NCHAHB_S), 3.24 (1H, dd, J 7.4, 11.5Hz, CHCHAHB_S), 3.10 (1H, dd, J 5.4, 14.2Hz, CHCHAHB_{Ar}), 3.00 (1H, dd, J 3.9, 11.5Hz, CHCHAHB_S), 2.93 (1H, dd, J 8.4, 14.2Hz, CHCHAHB_{Ar}) and 1.98 (3H, s, CH₃CO); m/z (ES, 60V) 531 ($M^+ + 1$).

25 **EXAMPLE 15**

N-Acetyl-D-thioproline-(O-2,6-difluorobenzyl)-L-tyrosine methyl ester

Caesium carbonate (0.609g, 1.87mmol) was added in one portion to a solution of Intermediate 2 (0.60g, 1.70mmol) in DMF (15ml). α-Bromo-2,6-difluorotoluene (0.387g, 1.87mmol) was then added and the reaction stirred for 16h at room temperature. The reaction was partitioned between ethyl acetate (50ml) and water (30ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2x50ml). The combined organic layers were washed with brine (50ml), dried over MgSO₄ and the solvent removed under vacuum to give a white, waxy solid (1.0g). Trituration with diisopropyl ether gave a white solid which was isolated by filtration, washed with diisopropyl ether and dried to give th

title compound (0.69g, 85%). δ H (DMSO-d₆, 390K) 7.84 (1H, br d, CONH), 7.52-7.42 (1H, m, OCH₂ArH), 7.15-7.06 (4H, m, OCH₂ArH + CHCH₂ArH), 6.93 (2H, d, \downarrow 8.4Hz, CHCH₂ArH), 5.13 (2H, s, OCH₂Ar), 4.82 (1H, dd, \downarrow 3.9, 7.2Hz, CH_αthiopro), 4.76 (1H, d, \downarrow 9.2Hz, NCHAHB_S), 4.56 (1H, dt, \downarrow 5.8, 8.2Hz, CH_αtyr), 4.38 (1H, d, \downarrow 9.3Hz, NCHAHB_S), 3.65 (3H, s, CO₃CH₃), 3.25 (1H, dd, \downarrow 7.4, 11.4Hz, CHCHAHB_S), 3.10-2.91 (3H, m, CHCH₂Ar + CHCHAHB_S) and 1.99 (3H, s, CH₃CO); m/z (ES) 479 (M⁺ + 1).

10 **EXAMPLE 16**

N-Acetyl-D-thioproline-(O-2,6-difluorobenzyl)-L-tyrosine

A solution of the compound of Example 15 (0.69g, 1.44mmol) in dioxane/methanol (1:1, 8ml) and water (6ml) was treated with lithium hydroxide monohydrate (72.6mg, 1.73mmol) in one portion. A further 1ml of dioxane was added to give a clear solution. The reaction was stirred for 1.5h at room temperature and then acidified to pH 4.5 with a few drops of glacial acetic acid to give a whiter precipitate. The bulk of solvent was removed *in vacuo*, water (5ml) added and the solid isolated by filtration, washed well with water (20ml), hexane (20ml) and dried under vacuum to give the title compound as a white solid (0.56g, 96%). δ H (DMSO-d₆, 390K) 7.69 (1H, br d, CONH), 7.53-7.42 (1H, m, OCH₂ArH), 7.16-7.06 (4H, m, OCH₂ArH + CHCH₂ArH), 6.93 (2H, d, \downarrow 8.6Hz, CHCH₂ArH), 5.12 (2H, s, OCH₂Ar), 4.82 (1H, dd, \downarrow 3.9, 7.3Hz, CH_αthiopro), 4.77 (1H, d, \downarrow 9.2Hz, NCHAHB_S), 4.50 (1H, dt, \downarrow 5.4, 8.3Hz, CH_αtyr), 4.37 (1H, d, \downarrow 9.0Hz, NCHAHB_S), 3.24 (1H, dd, \downarrow 7.4, 11.5Hz, CHCHAHB_S), 3.08 (1H, dd, \downarrow 5.4, 14.1Hz, CHCHAHB_{Ar}), 2.99 (1H, dd, \downarrow 3.9, 11.5Hz, CHCHAHB_S), 2.92 (1H, dd, \downarrow 8.5, 14.2Hz, CHCHAHB_{Ar}) and 1.98 (3H, s, CH₃CO); m/z (ES) 465 (M⁺ + 1).

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30 The following compounds of Examples 17 - 44 were prepared by a similar method to the compound of Example 16. Each starting ester was prepared by one of the procedures described for the preparation of the esters of Examples 1, 3, 5, 7, 9, 11, 13 or 15, using the appropriate thioproline starting material prepared according to the procedures of Intermedites 1-6.

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EXAMPLE 17**N-Acetyl-L-thioproline-(O-methyl)-L-tyrosin**

δH (DMSO-d⁶, 380K) 7.68 (1H, br s, CONH), 7.13 (2H, d, \downarrow 8.6Hz, ArH),
 6.82 (2H, d, \downarrow 8.7Hz, ArH), 7.13 (2H, d, \downarrow 8.6Hz, ArH), 6.82 (2H, d, \downarrow
 5 8.7Hz, ArH), 4.79 (1H, br m, CH_αthiopro), 4.74 (1H, d, \downarrow 9.2Hz,
 $\text{NCH}_\alpha\text{H}_\beta\text{S}$), 4.50 (1H, dt, \downarrow 8.2, 5.4Hz, CH_αtyr), 4.33 (1H, d, \downarrow 9.3Hz,
 $\text{NCH}_\alpha\text{H}_\beta\text{S}$), 3.73 (3H, s, OMe), 3.26 (1H, m, CH_{CH_α}H_βS), 3.10-3.03 (2H,
 m, CH_{CH_α}H_βS + CH_{CH_α}H_βAr), 2.92 (1H, dd, \downarrow 8.4, 1.41Hz, CH_{CH_α}H_βAr)
 and 1.94 (3H, s, COCH₃) (acid proton not observed at 380K); m/z (ESI,
 10 27V) 353 (M⁺ 1).

EXAMPLE 18**N-Acetyl-L-thioproline-(O-benzyl)-L-tyrosine**

m.p. 177-178°. δH (DMSO-d⁶, 400K) 7.6 (1H, br d, CONH), 7.43-7.29
 15 (5H, m, Ph), 7.13 (2H, d, \downarrow 8.6Hz, ArH), 6.90 (2H, d, \downarrow 8.6Hz, ArH), 5.07
 (2H, s, OCH₂Ph), 4.81 (1H, dd, \downarrow 7.6, 3.9Hz, CH_αthiopro), 4.73 (1H, d, \downarrow
 9.2Hz, NCH_αH_βS), 4.52 (1H, dt, \downarrow 8.2, 5.5Hz, CH_αtyr), 3.26 (1H, dd, \downarrow
 11.4, 7.4Hz, CH_{CH_α}H_βS), 3.09 (1H, dd, \downarrow 11.5, 3.7Hz, CH_{CH_α}H_βS), 3.07
 (1H, dd, \downarrow 14.2, 5.4Hz, CH_{CH_α}H_βAr), 2.92 (1H, dd, \downarrow 14.2, 8.2Hz,
 20 CH_{CH_α}H_βAr) and 1.95 (3H, s, COCH₃) (acid proton not observed at
 400K); m/z (ESI, 40V) 429 (M⁺ 1).

EXAMPLE 19**N-Acetyl-L-thioproline-(O-phenylethyl)-L-tyrosine**

δH (DMSO-d⁶, 400K) 7.55 (1H, br s, CONH), 7.29-7.15 (5H, m, Ph), 7.11
 (2H, d, \downarrow 8.7Hz, ArH), 6.81 (2H, d, \downarrow 8.7Hz, ArH), 4.81 (1H, dd, \downarrow 7.3,
 3.8Hz, CH_αthiopro), 4.74 (1H, d, \downarrow 9.3Hz, NCH_αH_βS), 4.47 (1H, m,
 CH_αtyr), 4.31 (1H, d, \downarrow 9.3Hz, NCH_αH_βS), 4.20 (2H, t, \downarrow 6.7Hz,
 OCH₂CH₂Ph), 3.26 (1H, dd, \downarrow 11.4, 7.4Hz, CH_{CH_α}H_βS), 3.10 (1H, dd, \downarrow
 30 11.5, 3.7Hz, CH_{CH_α}H_βS), 3.05 (1H, signal obscured, CH_{CH_α}H_βAr), 3.02
 (2H, t, \downarrow 6.7Hz, OCH₂CH₂Ph), 2.91 (1H, dd, \downarrow 14.1, 7.9Hz, CH_{CH_α}H_βAr)
 and 1.95 (3H, s, COCH₃) (acid proton not observed at 400K); m/z (ESI,
 15V), 443 (M⁺ 1).

EXAMPLE 20**N-Acetyl-L-thioproline-(O-benzoyl)-L-tyrosine**

m.p. 187-188°. δH (DMSO-d⁶, 400K) 8.11 (2H, d, J 8.0Hz, PhH), 7.73-7.68 (2H, m, CONH + PhH), 7.58 (2H, t, J 7.6Hz, PhH), 7.31 (2H, d, J 8.5Hz, ArH), 7.18 (2H, d, J 8.5Hz, ArH), 4.85 (1H, m, CH_αthiopro), 4.75 (1H, t, J 9.3Hz, NCH_AH_BS), 4.60 (1H, dt, J 5.4, 8.2Hz, CH_αtyr), 4.36 (1H, d, J 9.2Hz, NCH_AH_BS), 3.28 (1H, dd, J 11.4, 7.4Hz, CHCH_AH_BS), 3.18 (1H, dd, J 14.1, 5.5Hz, CHCH_AH_BAr), 3.11 (1H, dd, J 11.5, 3.8Hz, CHCH_AH_BS), 3.03 (1H, dd, J 14.1, 8.4Hz, CHCH_AH_BAr) and 1.97 (3H, s, COCH₃) (acid proton not observed at 400K); m/z (ESI, 27V) 443 (M⁺ + 1).

10 **EXAMPLE 21**

N-Acetyl-D-thioproline-(O-benzoyl)-L-tyrosine

δH (DMSO-d⁶, 400K) 8.11 (2H, d, J 7.8Hz, PhH), 7.8-7.68 (2H, m, CONH + PhH), 7.58 (2H, t, J 7.5Hz, PhH), 7.30 (2H, d, J 8.5Hz, ArH), 7.18 (2H, d, J 8.5Hz, ArH), 4.83 (1H, dd, J 7.2, 3.8Hz, CH_αthiopro), 4.77 (1H, d, J 9.2Hz, NCH_AH_BS), 4.57 (1H, dt, J 8.3, 5.5Hz, CH_αtyr), 4.38 (1H, d, J 9.2Hz, NCH_AH_BS), 3.26 (1H, dd, J 11.5, 7.3Hz, CHCH_AH_BS), 3.18 (1H, dd, J 14.1, 5.3Hz, CHCH_AH_BAr), 3.06-2.99 (2H, m, CHCH_AH_BS + - CHCH_AH_BAr) and 2.00 (3H, s, COCH₃) (acid proton not observed at 400K); m/z (ESI), 15V) 443 (M⁺ + 1).

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EXAMPLE 22

N-Acetyl-D-thioproline-(N-methyl)(O-benzyl)-L-tyrosine

δH (DMSO-d⁶, 400K) 7.42-7.29 (5H, m, Ph), 7.15 (2H, d, J 8.3Hz, ArH), 6.90 (2H, d, J 8.3Hz, ArH), 5.1 (1H, br m, CH_α thiopro), 5.06 (2H, s, 25 OCH₂Ph), 4.9 (1H, br m, CH_αtyr), 4.75 (1H, d, J 9.0Hz, NCH_AH_BS), 4.38 (1H, d, J 8.9Hz, NCH_AH_BS), 3.35-3.20 and 3.0-2.9 (4H, m, CHCH₂S + CHCH₂Ar), 2.90 (3H, br s, NMe) and 1.9 (3H, v br s, COCH₃) (acid proton not observed at 400K); m/z (ESI, 15V) 443 (M[±] + 1).

30 **EXAMPLE 23**

N-Acetyl-D-thioproline-(O-trifluoromethylsulphonyl)-L-tyrosine

δH (DMSO-d⁶, 400K) 7.8 (1H, br d, CONH), 7.40 (2H, d, J 8.8Hz, ArH), 7.30 (2H, d, J 8.8Hz, ArH), 4.79 (1H, dd, J 7.3, 3.8Hz, CH_αthiopro), 4.75 (1H, d, J 9.2Hz, NCH_AH_BS), 4.57 (1H, dt, J 8.7, 4.9Hz, CH_αtyr), 4.36 (1H, 35 d, J 9.2Hz, NCH_AH_BS), 3.26-3.18 (2H, m, CHCH_AH_BS +

$\text{CHCH}_\text{A}\text{H}_\text{B}\text{Ar}$), 3.04 (1H, dd, \downarrow 14.2, 8.8Hz, $\text{CHCH}_\text{A}\text{H}_\text{B}\text{Ar}$), 2.97 (1H, dd, \downarrow 11.6, 3.9Hz, $\text{CHCH}_\text{A}\text{H}_\text{B}\text{S}$) and 1.97 (3H, s, COCH₃) (acid proton not observed at 400K); m/z (ESI, 15V) 471 ($M^{+} + 1$).

5 **EXAMPLE 24**

N-Acetyl-D-thioproline-(O-tert.butyl)-L-tyrosine

δH (DMSO-d⁶, 300K) (2 rotameric species observed) 9.86 (1H, br s, CO₂H), 7.26-7.21 (m) and 7.05-7.02 (m) together (3H, NH and ArH), 6.86 (2H, d, \downarrow 8.32Hz, ArH), 4.95-4.31 (4H, m, CH_α-tyr, CH_α-thiopro and 10 NCH₂S), 3.22-2.88 (4H, m, CH₂Ar and CHCH₂S), 2.13 (s) and 2.10 (s) together (3H, CH₃CO) and 1.27 (9H, s, C(CH₃)₃); m/z (ESI, 60V) 395 ($M^{+} + 1$).

EXAMPLE 25

15 **N-Acetyl-L-thioproline-(O-2,6-dichlorobenzyl)-L-tyrosine**

δH (DMSO-d⁶, 390K) 7.65 (1H, br s, NH), 7.51-7.39 (3H, m, Cl₂-Ar-H), 7.17 (2H, ABd, \downarrow 8.7Hz, Ar-H), 6.95 (2H, ABd, \downarrow 8.7Hz, Ar-H), 5.25 (2H, s, CH₂OPh), 4.81 (1H, m, CH_α-thiopro), 4.74 (1H, d, \downarrow 9.2Hz, NCH_AH_BS), 4.54 (1H, ddd, \downarrow 13.6, 8.3, 5.4Hz, CH_α-tyr), 4.34 (1H, d, \downarrow 9.2Hz, 20 NCH_AH_BS), 3.28 (1H, dd, \downarrow 11.4, 7.4Hz, CHCH_AH_BAr) 3.09 (2H, m, CHCH₂S), 2.94 (1H, dd, \downarrow 14.1, 8.3Hz, CHCH_AH_BAr) and 1.96 (3H, s, MeCO). m/z (ESI, 60V) 497, 499 ($M^{+} + 1$).

EXAMPLE 26

25 **N-Acetyl-D-thioproline-(O-3,5-dichlorobenzyl)-L-tyrosine**

δH (DMSO-d⁶, 390K) 7.71 (1H, br d, NH), 7.45 (3H, s, Cl₂Ar-H), 7.15 (2H, m, Ar-H), 6.94 (2H, m, Ar-H), 5.10 (2H, s, CH₂OAr), 4.81 (1H, m, CH_α-thiopro), 4.76 (1H, d, \downarrow 9.2Hz, NCH_AH_BS), 4.49 (1H, m, CH_α-tyr), 4.36 (1H, d, \downarrow 9.2Hz, NCH_AH_BS), 3.26-2.91 (4H, m, CHCH₂S + 30 CHCH₂Ar), 1.97 (3H, s, MeCO). m/z (ESI, 60V) 497 ($M^{+} + 1$).

EXAMPLE 27

N-Acetyl-D-thioproline-(O-2-trifluoromethylbenzyl)-L-tyrosine

δH (DMSO-d⁶, 390K) 7.76-7.65 (4H, m, CF₃-ArH + NH), 7.57 (1H, t, \downarrow 8.0Hz, CF₃-Ar-H), 7.16 (2H, m, Ar-H), 6.92 (2H, m, Ar-H), 5.23 (2H, s,

CH_2OAr), 4.81 (1H, m, $\text{CH}\alpha$ -thiopro), 4.76 (1H, d, \downarrow 9.2Hz, NCHAHBS), 4.50 (1H, m, $\text{CH}\alpha$ tyr), 4.36 (1H, d, \downarrow 9.2Hz, NCHAHBS), 3.26-2.88 (4H, m, $\text{CHCH}_2\text{Ar} + \text{CHCH}_2\text{S}$), 1.97 (3H, s, MeCO). m/z (ESI, 80V), 497 ($\text{M}^{++} 1$).

5 **EXAMPLE 28**

N-Acetyl-D-thioproline-(O-2-dichlorobenzyl)-L-methoxytyrosine

δH (DMSO-d⁶) as a diastereomeric mixture 7.58 (1H, br s, NH), 7.51-7.40 (3H, m, Cl₂-Ar-H), 7.06 (1H, dd, \downarrow 8.3, 1.5Hz, MeOAr-H), 6.62 (1H, d, \downarrow 2.4Hz, MeOAr-H), 6.57 (1H, m, MeOAr-H), 5.27 (2H, s, CH_2OAr), 4.76 (d, \downarrow 9.2Hz) and 4.75 (d, \downarrow 9.3Hz) together (1H, NCHAHBS), 4.75 (1H, m, $\text{CH}\alpha$ -thiopro), 4.54 (1H, m, $\text{CH}\alpha$ tyr), 4.35 (d, \downarrow 9.3Hz) and 4.29 (d, \downarrow 9.2Hz) together (1H, NCHAHBS), 3.80 (3H, s, OMe), 3.29-2.80 (4H, m, $\text{CHCH}_2\text{Ar} + \text{CHCH}_2\text{S}$), 1.97 (s) and 1.95 (s) together (3H, MeCO). m/z (ESI, 60V), 527, 529 ($\text{M}^{++} 1$).

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15 δH (DMSO-d⁶) as a diastereomeric mixture 7.58 (1H, br s, NH), 7.51-7.40 (3H, m, Cl₂-Ar-H), 7.06 (1H, dd, \downarrow 8.3, 1.5Hz, MeOAr-H), 6.62 (1H, d, \downarrow 2.4Hz, MeOAr-H), 6.57 (1H, m, MeOAr-H), 5.27 (2H, s, CH_2OAr), 4.76 (d, \downarrow 9.2Hz) and 4.75 (d, \downarrow 9.3Hz) together (1H, NCHAHBS), 4.75 (1H, m, $\text{CH}\alpha$ -thiopro), 4.54 (1H, m, $\text{CH}\alpha$ tyr), 4.35 (d, \downarrow 9.3Hz) and 4.29 (d, \downarrow 9.2Hz) together (1H, NCHAHBS), 3.80 (3H, s, OMe), 3.29-2.80 (4H, m, $\text{CHCH}_2\text{Ar} + \text{CHCH}_2\text{S}$), 1.97 (s) and 1.95 (s) together (3H, MeCO). m/z (ESI, 60V), 527, 529 ($\text{M}^{++} 1$).

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EXAMPLE 29

N-Acetyl-D-thioproline-(O-4'-acetamidophenyl)-L-tyrosine

δH (DMSO-d⁶ 400K), 7.7 (1H, br d, CONH), 7.53 (2H, d, \downarrow 9.0Hz, ArH), 7.20 (2H, d, \downarrow 8.7Hz, ArH), 6.92 (2H, d, \downarrow 9.2Hz, ArH), 6.89 (2H, d, \downarrow 8.9Hz, ArH), 4.82 (1H, dd, \downarrow 7.5, 3.9Hz, $\text{CH}\alpha$ thiopro), 4.77 (1H, dt, \downarrow 9.2Hz, NCHAHBS), 4.54 (1H, dt, \downarrow 8.3, 5.4Hz, $\text{CH}\alpha$ tyr), 4.38 (1H, d, \downarrow 9.3Hz, NCHAHBS), 3.25 (1H, dd, \downarrow 11.5, 7.4Hz, CHCHAHBS), 3.08 (1H, dd, \downarrow 14.2, 5.4Hz, CHCHAHBAr), 2.99 (1H, dd, \downarrow 11.6, 4.0Hz, CHCHAHBS), 2.95 (1H, dd, \downarrow 14.2, 8.7Hz, CHCHAHBAr), 2.03 (3H, s, COCH₃) and 1.99 (3H, s, COCH₃) (acid proton and other amide proton not observed at 400K); m/z (ESI, 15V) 472 ($\text{M}^{++} 1$).

EXAMPLE 30

N-Acetyl-D-thioproline-(O-phenylaminocarbonyl)-L-tyrosine

30 δH (DMSO-d⁶, 300K), (2 rotameric species observed) 12.8 (1H, br s, CO₂H), 10.16 (1H, s, CONHPh), 8.49 (d, \downarrow 8.3Hz) and 8.23 (d, \downarrow 8.3Hz) together (1H, CONH), 7.50 (2H, d, \downarrow 8.1Hz, ArH), 7.31 (2H, t, \downarrow 7.9Hz, ArH), 7.24 (2H, d, \downarrow 8.5Hz, ArH), 7.12 (d, \downarrow 8.3Hz) and 7.11 (d, \downarrow 8.4Hz) together (2H, ArH), 7.04 (1H, t, \downarrow 7.3Hz, ArH), 4.80-4.67 (3H, m, $\text{CH}\alpha$ thiopro + NCHAHBS), 4.55-4.40 (1H, m, $\text{CH}\alpha$ tyr), 4.45 (d, \downarrow 8.8Hz)

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and 4.22 (d, \downarrow 9.8Hz) together (1H, NCH_AH_BS), 3.4-2.7 (4H, m, CHCH_AH_BAr + CHCH₂S), 2.05 (s) and 1.83 (s) together (3H, COCH₃) m/z (ESI, 15V) 458 (M^{++} 1).

5 **EXAMPLE 31**

N-Acetyl-D-thioproline-(O-2'-nitrophenyl)-L-tyrosine

- δH (DMSO-d⁶ 400K), 7.97 (1H, dd, \downarrow 8.1, 1.6Hz, (NO₂)ArH), 7.7 (1H, v br d, CONH), 7.64 (1H, ddd, \downarrow 8.4, 7.5, 1.7Hz, (NO₂)ArH), 7.33 (1H, ddd, \downarrow 8.1, 7.5, 1.2 Hz, (NO₂)ArH), 7.27 (2H, d, \downarrow 8.7Hz, ArH), 7.11 (1H, dd, \downarrow 8.4, 1.2Hz, (NO₂)ArH), 6.97 (2H, d, \downarrow 8.7Hz, ArH), 4.82 (1H, dd, \downarrow 7.4, 4.0Hz, CH_Athiopro), 4.77 (1H, d, \downarrow 9.2Hz, NCH_AH_BS), 4.56 (1H, dt, \downarrow 8.5, 5.4Hz, CH_Atyr), 4.38 (1H, d, \downarrow 9.2Hz, NCH_AH_BS), 3.25 (1H, dd, \downarrow 11.5, 7.4Hz, CHCH_AH_BS), 3.16 (1H, dd, \downarrow 14.1, 5.3Hz, CHCH_AH_BAr), 3.01 (1H, dd, \downarrow 11.5, 3.9Hz, CHCH_AH_BS), 2.98 (1H, signal obscured, CHCH_AH_BAr) and 1.99 (3H, s, COCH₃) (acid proton not observed at 400K); m/z (ESI, 27V) 460 (M^{++} 1).

EXAMPLE 32

N-Acetyl-D-thioproline-S,S-dioxide(O-benzyl)-L-tyrosine

- δH (DMSO-d⁶ 400K), 7.793(1H, br d, CONH), 7.44-7.30 (5H, m, Ph), 7.13 (2H, d, \downarrow 8.7Hz, ArH), 6.93 (2H, d, \downarrow 8.7Hz, ArH), 5.19 (1H, dd, \downarrow 8.9, 4.9Hz, CH_Athiopro), 5.08 (2H, s, OCH₂Ph), 4.96 (1H, dt, \downarrow 11.9Hz, NCH_AH_BS), 4.51 (1H, dt, \downarrow 8.2, 5.5Hz, CH_Atyr), 4.29 (1H, d, \downarrow 11.8Hz, NCH_AH_BS), 3.56 (1H, dd, \downarrow 13.6, 8.9Hz, CHCH_AH_BS), 3.19 (1H, dd, \downarrow 13.6, 5.0Hz, CHCH_AH_BS), 3.09 (1H, dd, \downarrow 14.2, 5.5Hz, CHCH_AH_BAr), 2.91 (1H, dd, \downarrow 14.2, 8.4Hz, CHCH_AH_BAr) and 2.03 (3H, s, COCH₃) (acid proton not observed at 400K); m/z (ESI, 27V) 461 (M^{++} 1).

EXAMPLE 32

N-Acetyl-L-thioproline-(O-2,6-dichlorobenzoyl)-D-tyrosine

- δH (DMSO-d⁶ 400K), 7.75 (1H, br d, CONH), 7.63-7.54 (3H, m, ClArH), 7.35 (2H, d, \downarrow 8.7Hz, ArH), 7.20 (2H, d, \downarrow 8.6Hz, ArH), 4.83 (1H, dd, \downarrow 7.4, 3.9Hz, CH_Athiopro), 4.77 (1H, d, \downarrow 9.2Hz, NCH_AH_BS), 4.57 (1H, m, CH_Atyr), 4.38 (1H, d, \downarrow 9.3Hz, NCH_AH_BS), 3.25 (1H, dd, \downarrow 11.5, 7.4Hz, CHCH_AH_BS), 3.20 (1H, dd, \downarrow 14.3, 5.4Hz, CHCH_AH_BAr), 23.08-3.00 (2H,

m, $\text{CHCH}_2\text{H}_\text{B}\text{S}$ + $\text{CHCH}_2\text{H}_\text{B}\text{Ar}$) and 1.99 (3H, s, COCH_3) (acid proton not observed at 400K); m/z (ESI, 15V) 511 ($\text{M}^{++} 1$).

EXAMPLE 33

5 **N-Acetyl-D-thioproline-S-oxide-(O-2,6-dichlorobenzyl)-L-tyrosine**
 δ H (DMSO-d⁶ 390K), 8.04 (1H, br s, NH), 7.51 (1H, d, \downarrow 9.3Hz, $\text{Cl}_2\text{-Ar-H}$),
 7.50 (1H, d, \downarrow 6.5, $\text{Cl}_2\text{-Ar-H}$), 7.42 (1H, dd, \downarrow 9.3, 6.5Hz, $\text{Cl}_2\text{-Ar-H}$), 7.16
 (1H, d, \downarrow 8.6Hz, Ar-H), 6.97 (2H, d, \downarrow 8.6Hz, Ar-H), 5.26 (2H, s, CH_2OAr),
 5.16 (1H, m, $\text{CH}_\alpha\text{thiopro}$), 4.99 (1H, d, \downarrow 12.9Hz, $\text{NCH}_2\text{H}_\text{B}\text{SO}$), 4.51 (1H,
 10 m, $\text{CH}_\alpha\text{tyr}$), 4.14 (1H, d, \downarrow 12.9Hz, $\text{NCH}_2\text{H}_\text{B}\text{SO}$), 3.21-2.85 (4H, m,
 CHCH_2SO + CHCH_2Ar), 2.05 (3H, s, MeCO); m/z (ESI, 60V) 513 ($\text{M}^{++} 1$).

EXAMPLE 34

15 **N-Acetyl-D-thioproline-S,S-dioxide-(O-2,6-dichlorobenzyl)-L-tyrosine**
 δ H (DMSO-d⁶ 390K), 8.04 (1H, b s, NH), 7.51 (1H, d, \downarrow 9.3Hz, $\text{Cl}_2\text{-Ar-H}$),
 7.50 (1H, d, \downarrow 6.5, $\text{Cl}_2\text{-Ar-H}$), 7.42 (1H, dd, \downarrow 9.3, 6.5Hz, $\text{Cl}_2\text{-Ar-H}$), 7.16
 (2H, ABd, \downarrow 8.6Hz, Ar-H), 6.96 (2H, ABd, \downarrow 8.6Hz, Ar-H), 5.26 (2H, s,
 CH_2OAr), 5.19 (1H, dd, \downarrow 9.2, 5.0Hz, $\text{CH}_\alpha\text{thiopro}$), 4.98 (1H, d, \downarrow 11.9Hz,
 N $\text{CH}_2\text{H}_\text{B}\text{SO}_2$), 4.51 (1H, m, $\text{CH}_\alpha\text{tyr}$), 4.31 (1H, d, \downarrow 11.9Hz,
 20 N $\text{CH}_2\text{H}_\text{B}\text{SO}_2$), 3.20-2.93 (4H, m, CHCH_2SO_2 + CHCH_2Ar), 2.05 (3H, s,
 MeCO); m/z (ESI, 60V) 529 ($\text{M}^{++} 1$).

EXAMPLE 35

25 **N-Acetyl-D-thioproline-O[1-(2-methylnaphthyl)methyl]-L-tyrosine**
 δ H (DMSO-d⁶ 390K), 8.09 (1H, d, \downarrow 8.4Hz, NapH), 7.88 (1H, d, \downarrow 7.9Hz,
 Nap-H), 7.83 (1H, d, \downarrow 8.4Hz, Nap-H), 7.67 (1H, br s, NH), 7.54-7.42 (3H,
 m, NapH), 7.17 (2H, ABd, \downarrow 8.6Hz, Ar-H), 6.98 (2H, ABd, \downarrow 8.6Hz, Ar-H),
 5.49 (2H, s, CH_2OAr), 4.83 (1H, dd, \downarrow 7.2, 3.9Hz, $\text{CH}_\alpha\text{thiopro}$), 4.78
 N $\text{CH}_2\text{H}_\text{B}\text{S}$, 4.48 (1H, m, $\text{CH}_\alpha\text{tyr}$), 4.38 (1H, d, \downarrow 9.2Hz, N $\text{CH}_2\text{H}_\text{B}\text{S}$), 3.25-
 30 2.90 (4H, m, CHCH_2S + CHCH_2Ar) and 1.98 (3H, s, MeCO); m/z (ESI,
 60V) 493 ($\text{M}^{++} 1$).

EXAMPLE 36

N-Acetyl-D-thioproline-(O- α -methyl benzyl)-L-tyrosine

δ H (DMSO-d⁶ 390K), 7.64 (1H, br d, NH), 7.40-7.20 (5H, m, Ph), 7.05 (2H, d, \downarrow 8.5Hz, Ar-H), 6.81 (2H, m, \downarrow 8.5, Ar-H), 5.39 (1H, q, \downarrow 6.4Hz, CHM), 4.76 (1H, m, CH₂thiopro), 4.75 (1H, d, \downarrow 9.1Hz, NCH_AH_BS), 4.44 (1H, m, CH₂tyr), 4.33 (1H, d, \downarrow 9.1Hz, NCH_AH_BS), 3.22-2.82 (4H, m, CHCH₂SO + 5 CHCH₂Ar), 1.95 (3H, s, MeCO) and 1.55 (3H, d, \downarrow 6.4Hz, CHMe; m/z (ESI, 60V) 443 ($M^{++} 1$).

EXAMPLE 37

N-Acetyl-D-thioproline-(O-2,4,6-trichlorobenzoyl)-L-tyrosine

10 δ H (DMSO-d⁶ 390K), 7.80 (1H, br d, NH), 7.77 (2H, s Cl₃Ar-H), 7.35 (2H, ABd, \downarrow 8.6Hz, Ar-H), 7.20 (2H, ABd, \downarrow 8.6Hz, Ar-H), 4.81 (1H, m, CH₂thiopro), 4.76 (1H, d, \downarrow 19.2Hz, NCH_AH_BS), 4.57 (1H, m, CH₂tyr), 4.38 (1H, d, \downarrow 9.2Hz, NCH_AH_BS), 3.35-2.95 (4H, m, CHCH₂S + CHCH₂Ar) and 1.99 (3H, s, MeCO); m/z (ESI, 60V) 544 ($M^{++} 1$).

15

EXAMPLE 38

N-Acetyl-D-thioproline-(O-phenylsulphonyl)-L-tyrosine

20 δ H (DMSO-d⁶ 400K), 7.88-7.62 (6H, m, Ph + CONH), 7.22 (2H, d, \downarrow 8.7Hz, ArH), 6.97 (2H, d, \downarrow 8.7Hz, ArH), 4.80 (1H, dd, \downarrow 7.4, 3.9Hz, CH₂thiopro), 4.76 (1H, d, \downarrow 9.1Hz, NCH_AH_BS), 4.52 (1H, dt, \downarrow 8.6, 5.4Hz, CH₂tyr), 4.36 (1H, d, \downarrow 9.6Hz, NCH_AH_BS), 3.23 (1H, dd, \downarrow 11.5, 7.4Hz, CHCH_AH_BS), 3.13 (1H, dd, \downarrow 14.2, 5.4Hz, CHCH_AH_BAr), 3.00-2.93 (2H, m, CHCH_AH_BS + CHCH_AH_BAr) and 1.98 (3H, s, COCH₃) (acid proton not observed at 400K); m/z (ESI, 15V) 479 ($M^{++} 1$).

25

EXAMPLE 39

N-Acetyl-D-thioproline-(O-benzyl)-3,5-dibromo-L-tyrosine

30 δ H (DMSO-d⁶ 400K), 7.85 (1H br d; CONH), 7.57-7.36 (7H, m, ArH), 4.83 (1H, dd, \downarrow 7.4, 3.9Hz, CH₂thiopro), 4.77 (1H, d, \downarrow 9.1Hz, NCH_AH_BS), 4.55 (1H, m, CH₂tyr), 4.39 (1H, d, \downarrow 9.2Hz, NCH_AH_BS), 3.28 (1H, dd, \downarrow 11.6, 7.4Hz, CHCH_AH_BS), 3.15 (1H, dd, \downarrow 14.2, 5.3Hz, CHCH_AH_BAr), 3.02 (1H, dd, \downarrow 11.6, 3.8Hz, CHCH_AH_BS), 2.97 (1H, dd, \downarrow 14.2, 88Hz, CHCH_AH_BAr) and 2.01 (3H, s, COCH₃) (acid proton not observed at 400K); m/z (ESI, 15V) 585 ($M^{++} 1$).

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EXAMPLE 40N-Acetyl-D-thioproline-(O-benzylaminocarbonyl)-L-tyr sine

δH (DMSO-d⁶ 400K), 7.65 (1H, br, CONH), 7.56 (1H, br, CONH), 7.35-7.25 (5H, m, Ph), 7.20 (2H, d, J 8.5Hz, ArH), 7.00 (2H, d, J 8.5Hz, ArH), 5 4.82 (1H, dd, J 7.4, 4.0Hz, CH_αthiopro), 4.66 (1H, d, J 9.2Hz, NCH_AH_BS), 4.48 (1H, m, CH_αtyr), 4.37 (1H, d, J 9.3Hz, NCH_AH_BS), 4.32 (2H, d, J 6.1Hz, NCH₂Ph), 3.24 (1H, dd, J 11.5, 7.4Hz, CHCH_AH_BS), 3.13 (1H, dd, J 14.1, 5.3Hz, CHCH_AH_BAr), 3.03 (1H, dd, J 11.5, 3.9Hz, CHCH_AH_BS), 10 2.98 (1H, dd, J 14.1, 7.9Hz, CHCH_AH_BAr) and 1.98 (3H, s, COCH₃) (acid proton not observed at 400K); m/z (ESI, 15V) 472 (M⁺⁺ 1).

EXAMPLE 41N-Acetyl-D-thioproline-(O-2'-acetamidophenyl)-L-tyrosine

δH (DMSO-d⁶ 400K), 8.76 (1H, br s, PhNHCO), 7.96-7.92 (1H, m, 15 (CONH)ArH), 7.68 (1H, br d, CONH), 7.22 (2H, d, J 8.7Hz, ArH), 7.10-7.03 (2H, m, (CONH) ArH), 6.91 (2H, d, J 8.7Hz, ArH), 6.88-6.84 (1H, m, (CONH) ArH), 4.83 (1H, dd, J 7.3, 3.9Hz, CH_αthiopro), 4.77 (1H, d, J 9.2Hz, NCH_AH_BS), 4.54 (1H, dt, J 8.4, 5.3Hz, CH_αtyr), 4.38 (1H, d, J 9.2Hz, NCH_AH_BS), 3.26 (1H, dd, J 11.5, 7.4Hz, CHCH_AH_BS), 3.14 (1H, 20 dd, J 14.1, 5.4Hz, CHCH_AH_BAr), 3.02 (1H, dd, J 11.6, 3.9Hz, CHCH_AH_BS), 2.96 (1H, dd, J 14.1, 8.5Hz, CHCH_AH_BAr), 2.03 (3H, s, COCH₃) and 1.99 (3H, s, COCH₃) (acid proton not observed at 400K); m/z (ESI, 30V) 472 (M⁺⁺ 1).

25 EXAMPLE 42N-Acetyl-D-thioproline-(O-2,6-dichlorobenzyl)-3-chloro-L-tyrosine

δH (DMSO-d⁶ 400K), 7.75 (1H, br d, CONH), 7.52-7.40 (3H, m, Cl₂ArH), 7.27-7.14 (3H, m, ClArH), 5.34 (2H, s, OCH₂Ar), 4.83 ((1H, dd, J 7.3, 3.9Hz, CH_αthiopro), 4.77 (1H, d, J 9.2Hz, NCH_AH_BS), 4.53 (1H, dt, J 8.5, 30 5.2Hz, CH_αtyr), 4.38 (1H, d, J 9.2Hz, NCH_AH_BS), 3.26 (1H, dd, J 11.4, 7.3Hz, CHCH_AH_BS), 3.11 (1H, dd, J 14.2, 5.4Hz, CHCH_AH_BAr), 3.01 (1H, dd, J 11.5, 3.9Hz, CHCH_AH_BS), 2.94 (1H, dd, J 14.1, 8.5Hz, CHCH_AH_BAr) and 2.00 (3H, s, COCH₃) (acid proton not observed at 400K); m/z (ESI, 30V) 531 (M⁺⁺ 1).

35

EXAMPLE 43

N-Acetyl-D-thioproline-(N-methyl)(O-benzyl)-L-tyrosine

δ H (DMSO-d⁶ 400K) 7.44-7.29 (5H, m, Ph), 7.15 (2H, d, \downarrow 8.7Hz, ArH), 6.92 (2H, d, \downarrow 8.7Hz, AH), 5.16 (1H, m, CH₂thiopro), 5.08 (2H, s, OCH₂Ph), 4.96 (1H, dd, \downarrow 9.9, 5.3Hz, CH₂tyr), 4.77 (1H, d, \downarrow 9.2Hz,

5 NCHA₂HBS), 4.37 (1H, d, \downarrow 9.2Hz, NCHA₂HBS), 3.3 (1H, v br m, CHCHA₂HBS), 3.21 (1H, dd, \downarrow 14.6, 5.3Hz, CHCHA₂H₂Ar), 3.01 (1H, dd, \downarrow 14.6, 9.9Hz, CHCHA₂H₂Ar), 2.8 (1H, v br m, CHCHA₂HBS), 2.93 (3H, s, NMe) and 1.84 (3H, br s, COCH₃) (acid proton not observed at 400K); m/z (ESI, 60V) 443 (M^{++} 1).

10

EXAMPLE 44N-Acetyl-L-thioproline-(O-2,6-dichlorobenzoyl)- α -methyl-L-tyrosine

δ H (DMSO-d⁶ 390K), 7.64-7.55 (3H, m, CIArH), 7.48 (1H, br s, CONH), 7.28 (2H, d, \downarrow 8.6Hz, ArH), 7.19 (2H, d, \downarrow 8.6Hz, ArH), 4.87 (1H, dd, \downarrow 7.2,

15 3.6Hz, CH₂thiopro), 4.76 (1H, d, \downarrow 9.2Hz, NCHA₂HBS), 4.38 (1H, d, \downarrow 9.2Hz, NCHA₂HBS), 3.30 (2H, s, CH₂Ar), 3.30 (1H, signal obscured CHCHA₂HBS), 3.17 (1H, dd, \downarrow 11.5, 3.6Hz, CHCHA₂HBS), 2.02 (3H, s, COCH₃) and 1.48 (CMe) (acid proton not observed at 400K); m/z (ESI, 60V) 525 (M^{++} 1).

20

EXAMPLE 45N-(4'-Acetamidophenylacetyl)-D-thioproline-(O-benzyl)-L-tyrosine methyl ester

EDC. HCl (158mg, 0.82mmol) was added to a solution of Intermediate 10

25 (300mg, 0.75mmol), 4-acetamidophenylacetic acid (159mg, 0.82mmol), and HOBT (122mg, 0.90mmol) in DMF (5ml) and the reaction stirred for 4h at room temperature. The DMF was removed *in vacuo* and the residue partitioned between ethyl acetate (20ml) and 5% aqueous Na₂CO₃ (20ml). The aqueous phase was separated and extracted with ethyl acetate (2 x 10ml). The combined organic phases were washed with brine (10ml), and dried (Na₂SO₄) to give an oil which was purified by chromatography (SiO₂, ethyl acetate) to give the title compound as a colourless foam (320mg, 74%). δ H (DMSO-d⁶) (2 rotameric species observed). 9.87 (1H, s, ArNHCO), 8.66 (br d, \downarrow 7.9Hz) and 8.31 (br d, \downarrow 7.9Hz) together (1H, NH), 7.51-6.86 (13H, m, Ar-H), 5.04 (s) and 5.02 (s) together (2H, CH₂OAr), 4.78 (2H, m, CH₂thiopro + NCHA₂HBS), 4.47 (1H, m, CH₂tyr), 4.46 (m) and

4.26 (m) tog ther (1H, NCH₂HBS), 3.62 (3H, s, CO₂Me), 3.52-2.68 (4H, m, CHCH₂S + CHCH₂Ar) and 2.02 (3H, s, COMe). m/z (ESI, 15V) 576 (M^{++} 1).

5 The following ester was prepared in a similar manner:

N-Phenylacetyl-D-thioproline-(O-benzyl)-L-tyrosine methyl ester

δ H (CDCl₃/CD₃OD 2:1) 7.18-6.61 (14H, m, Ar-H), 4.78 (2H, s, CH₂OPh), 4.72 (2H, m, CH_α-thiopro + NCH₂HBS), 3.45 (3H, s, CO₂Me) and 3.20-2.67 (4H, m, CHC₂Ar + CHCH₂S). m/z (ESI, 15V) 519 (M^{++} 1).

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EXAMPLE 46

N-(4'-Acetamidophenylacetyl)-D-thioproline-(O-benzyl)-L-tyrosine

A solution of the compound of Example 46 (275mg, 0.48mmol) in MeOH (2ml), dioxan (2ml), DMF (2ml) and water (3ml) was treated with LiOH

15

(24mg, 0.57mmol) and stirred at room temperature for 3h, acidified with glacial acetic acid and concentrated *in vacuo*. The residue was triturated with water and the off-white solid isolated by filtration and dried *in vacuo* to give the title compound (150mg, 56%). δ H (DMSO-d⁶) (2 rotameric species observed) 9.89 (1H, s, NHCOMe), 8.32 (br s) and 7.98 (br s),

20

together (1H, NH), 7.52-6.82 (13H, Ar-H), 5.02 (s) and 4.97 (s) together (2H, CH₂OPh), 4.82 (2H, m, CH_αthiopro + CH_αtyr), 4.49-4.23 (2H, m, NCH₂S) and 3.56-2.70 (6H, m, CHCH₂Ar, COCH₂Ar, CHCH₂S). m/z (ESI, 60V) 562 (M^{++} 1).

25

The following compounds of Examples 47 - 61 were prepared in a similar manner to the compound of Example 46. Each starting ester was prepared according to the method of compound of Example 46.

EXAMPLE 47

30

N-Benzoyl-D-thioproline-(O-benzyl)-L-tyrosine

δ H (CD₃OD) 8.12 (1H, br s, NH), 7.54-7.26 (10H, m, Ar-H), 7.11 (2H, ABd, J 8.5Hz, CHCH₂Ar-H), 6.86 (2H, ABd, J 8.5Hz, CHCH₂Ar-H), 5.01 (1H, m, CH_αthiopro), 4.99 (2H, s, OCH₂Ph), 4.72-4.47 (3H, m, CH_αtyr + NCH₂S) and 3.22-2.79 (4H, m, CHCH₂S + CHCH₂Ar). m/z (ESI, 15V) 491 (M^{++} 1).

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EXAMPLE 48

N-(2-Chloro-4-nitrobenzyl)-D-thioproline-(O-benzyl)-L-tyrosin

δ H (CD₃OD) (2 rotameric species observed) 8.36 (d, \downarrow 2.1Hz) and 8.32 (d, \downarrow 2.1Hz) together (1H, NO₂-Ar-H), 8.28 (d, \downarrow 2.1Hz) and 8.25 (d, \downarrow 2.1Hz) together (1G, NO₂-Ar-H), 7.65 (0.5H, d, \downarrow 8.4Hz, NO₂-Ar-H), 7.42-

5 7.23 (5.5H, m, PhCH₂O + NO₂Ar-H), 7.15 (d, \downarrow 8.7Hz), and 7.05 (d, \downarrow 8.7Hz) together (2H, ar-H), 6.88 (2H, m, Ar-H), 5.04 and 5.01 together (2H, s, CH₂OPh), 5.03 (1H, m, CH α Thiopro), 4.71-4.29 (3H, m, CH α tyr + NCH₂S) and 3.37-2.68 (4H, m, CHCH₂S + CHCH₂Ar). m/z (ESI, 15V), 570 (M^{++} 1).

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EXAMPLE 49N-(Phenylaminocarbonyl)-D-thioproline-(O-benzyl)-L-tyrosine

δ H (DMSO- δ d) 8.63 (1H, s, NHPh), 8.07 (1H, d, \downarrow 8.2Hz, NH), 7.53-7.22 (9H, m, Ar-H), 7.11 (2H, ABd, \downarrow 8.4Hz, Ar-H), 6.97 (1H, m, Ar-H), 6.80 (2H,

15 ABd, \downarrow 8.4Hz, Ar-H), 4.97 (2H, CH₂OPh), 4.96 (1H, m, CH α Thiopro), 4.80 (1H, d, \downarrow 8.8Hz, NCH₂HBS), 4.43 (1H, d, \downarrow 8.8Hz, NCH₂HBS), 4.42 (1H, m, CH α -tyr) and 3.05-2.83 (4H, m, CHCH₂Ar + CHCH₂S). m/z (ESI, 60V), 506 (M^{++} 1).

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EXAMPLE 50N-(tert-Butoxycarbonyl)-D-thioproline-(O-benzyl)-L-tyrosine

δ H (DMSO- δ d) 8.22 (1H, br s, NH), 7.46-7.29 (5H, m, Ph), 7.11 (2H, ABd, \downarrow 8.4Hz, Ar-H), 6.89 (2H, ABd, \downarrow 8.4Hz, Ar-H), 5.05 (2H, s, CH₂OPh), 4.57 (1H, d, \downarrow 9.0Hz, NCH₂HBS), 4.49 (2H, m, CH α Thiopro + CH α tyr), 4.22 (1H,

25 d, \downarrow 9.0Hz, NCH₂HBS), 3.18-2.53 (4H, m, CHCH₂Ar + CHCH₂S) and 1.33 (9H, s, tBu). m/z (ESI, 15V) 487 (M^{++} 1).

EXAMPLE 51N-Phenylacetyl-D-thioproline-(O-benzyl)-L-tyrosine

30 δ H (DMSO-d δ) 2 rotameric species observed. 6.66-6.05 (14H, m, Ar-H), 4.23 (s) and 4.19 (s) together (2H, CH₂OPh), 4.03 (1H, m, CH α Thiopro), 3.98-3.65 (3H, m, CH α tyr-NCH₂S), 2.72-2.01 (6H, m, COCH₂Ph, CHCH₂Ar, CHCH₂S). m/z (ESI, 15V) 505 (M^{++} 1).

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EXAMPLE 52N-Methylsulphonyl-D-thioproline-(O-benzyl)-L-tyrosine

δH (DMSO-d⁶) 8.09 (1H, d, J 8.2Hz, NH), 7.46-7.31 (5H, m, Ar-H), 7.12 (2H, ABd, J 8.5Hz, Ar-H), 6.88 (2H, ABd, J 8.5Hz, Ar-H), 5.05 (2H, s, CH₂OPh), 4.73 (1H, d, J 10.2Hz, NCH₂HBS), 4.72 (1H, m, CH_αthiopro), 4.40 (1H, m, CH_α-tyr), 4.29 (1H, d, J 10.2Hz), 32.25 (1H, dd, J 11.4, 7.6Hz, CHCH₂HBS), 3.03 (3H, s, SO₂Me) and 3.02-2.86 (3H, m, CHCH₂HBS, CHCH₂Ar). m/z (ESI, 15V), 465 (M⁺+ 1).

EXAMPLE 53

N-Dimethylacetyl-D-thioproline-(O-2,6-dichlorobenzyl)-L-tyrosine

10 Found C, 54.25; H, 4.93; N, 5.22. C₂₄H₂₆Cl₂N₂O₅S. 0.3H₂O requires C, 54.24; H, 5.06; N, 5.27. m/z (ESI, 60V) 525, 527 (M⁺+ 1).

EXAMPLE 54

N-(4-tert-Butoxycarbonylamino)butyryl-D-thioproline-(O-2,6-dichlorobenzyl)-L-tyrosine

15 δH (DMSO-d⁶) 8.39 (br s,) and 8.12 (br s) together (1H, NHBOC), 7.57-6.93 (7H, m, Ar-H), 6.80 (1B, br s, NH), 5.18 (2H, s, CH₂OPh), 4.83-4.20 (4H, m, CH_αthiopro + CH_αtyr + NCH₂S), 3.20-2.71 (6H, m, CHCH₂Ar + CHCH₂S + CH₂CO), 2.34 (2H, m, CH₂N, 1.61 (2H, m, CH₂CH₂N) and 20 1.36 (9H, s, tBu). m/z (ESI, 60V) 662 (M⁺+ 23).

EXAMPLE 55

N-(4-Amino)butyryl-D-thioproline-(O-2,6-dichlorobenzyl)-L-tyrosine hydrochloride

25 δH (DMSO-d⁶) 7.96 *1H, br s, NH), 7.51-7.38 (3H, m, Cl₂-Ar-H), 7.18 (2H, ABd, J 8.7Hz, ArH), 6.95 (2H, ABd, J 8.7Hz, Ar-H), 5.25 (2H, s, CH₂OPh), 4.90 (1H, dd, J 7.4, 4.1Hz, CH_αthiopro), 4.54 (1H, d, J 9.2Hz, NCH₂HBS), 4.50 (1H, ddd, J 13.7, 8.4, 5.4Hz, CH tyro), 4.41 (1H, d, J 9.2Hz, NCH₂HBS), 3.29-2.87 (6H, m, CHCH₂Ar + CHC₂S + CH₂CO), 2.49 (2H, 30 m, CH₂NH₂) AND 1.88 (2H, m, CH₂CH₂N). M/Z (ESI, 60V) 540, 542 (M⁺+1).

EXAMPLE 56

N-(3-tert-Butoxycarbonylamino)propionyl-D-thioproline-(O-2,6-dichlorobenzyl)-L-tyrosine

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δ H (DMSO-d⁶) 8.35 (br s) and 8.08 (br s) together (1H, NH), 7.56-7.43 (3H, m, Cl₂-Ar-H), 7.15 (2H, br d, Ar-H), 6.96 (2H, ABd, \downarrow 6.4Hz, Ar-H), 6.61 (br s) and 6.49 (br s) together (1H, NHCOO+ Bu), 5.19 (2H, s, CH₂OPh), 4.74 (2H, m, CH α -thiopro + NCH_AH_BS), 4.49-4.28 (2H, m, CH α -tyr + NCH_AH_BS), 3.32-2.71 (8H, n, CHCH₂Ar + CHCH₂S + COCH₂ + CH₂NH) and 1.36 (9H, s, + tBu). m/z (ESI, 30V) 648, 650 (M^+ + Na).

EXAMPLE 57

N-(3-Amino)propionyl-D-thioproline-(O-2,6-dichlorobenzyl)-L-tyrosine hydrochloride

10 δ H (DMSO-d⁶) 8.02 (1H, br s, NH), 7.51-7.39 (3H, m, Cl₂-r-H), 7.18 (2H, ABd, Ar-H), 6.96 (2H, ABd, Ar-H), 5.25 (2H, s, CH₂OPh), 4.91 (1H, dd, 7.3, 3.9Hz, CH α -thiopro), 4.77 (1H, d, \downarrow 9.1Hz, NCH_AH_BS), 4.52 (1H, m, CH α -tyr), 4.32 (1H, d, \downarrow 9.1Hz, NCH_AH_BS), 3.30-2.52 (8H, m, CHCH₂Ar + 15 CHCH₂S + CH₂CO + CH₂NH₂). m/z (ESI, 60V) 526, 528 (M^+ +1).

EXAMPLE 58

N-(3-Carboxy)propionyl-D-thioproline-(O-2,6-dichlorobenzyl)-L-tyrosine methyl ester

20 δ H (DMSO-d⁶) 7.88 (1H, br s, NH), 7.51-7.38 (3H, m, Cl₂-Ar-H), 7.14 (2H, ABd, \downarrow 8.7Hz, Ar-H), 6.97 (2H, ABd, \downarrow 8.7Hz, Ar-H), 5.26 (2H, s, CH₂OPh), 4.88 (1H, dd, \downarrow 7.3, 3.8Hz, CH α -thiopro), 4.80 (1H, d, \downarrow 9.1Hz, NCH_AH_BS), 4.56 (1H, ddd, \downarrow 14.0, 8.4, 5.7Hz, CH α -tyr), 4.40 (1H, d, \downarrow 9.1Hz, NCH_AH_BS), 3.65 (3H, s, CO₂Me), 3.27-2.91 (4H, m, CHCH₂Ar+CHCH₂S) and 2.55 (4H, m, CH₂CH₂CO₂H). m/z (ESI, 60V) 569, 571 (M^+ + 1).

EXAMPLE 59

N-(3-Carboxy)propionyl-D-thioproline-(O-2,6-dichlorobenzyl)-L-tyrosine

30 δ H (DMSO-d⁶) 7.70 (1H, br s, NH), 7.52-7.39 (3H, m, Cl₂-Ar-H), 7.16 (2H, ABd, \downarrow 8.6Hz, Ar-H), 6.96 (2H, ABd, \downarrow 8.6Hz, Ar-H), 5.25 (2H, s, CH₂OPh), 4.88 (1H, dd, \downarrow 7.4, 3.8Hz, CH α -thiopro), 4.81 (1H, d, \downarrow 9.1Hz, NCH_AH_BS), 4.49 (1H, m, CH α -tyr), 4.39 (1H, d, \downarrow 9.1Hz, NCH_AH_BS), 3.26-2.88 (4H, m, CHCH₂Ar + CHCH₂S), 2.57 (4H, m, CH₂CH₂CO₂H). m/z (ESI, 60V) 555, 35 557 (M^+ + 1).

EXAMPLE 60**N-(2-Methylpr pyl)oxycarb nyl-D-thiopr line-(O-benzyl)-L-tyr sine**

δH (DMSO-d⁶, 390K) 7.64 (1H, br d, NH), 7.37 (5H, m, Ph-H), 7.11 2H,
 5 ABd, ↓ 8.7Hz, Ar-H), 6.90 (2H, ABd, ↓ 8.7Hz, Ar-H), 5.07 (2H, s, CH₂OPh),
 4.69 (1H, m, CHα-thiopro), 4.69 (1H, d, ↓ 9.0Hz, NCHAHBS), 4.46 (1H, m,
 CHαtyr), 4.32 (1H, d, ↓ 9.0Hz, NCHAHBS), 3.82 (2H, d, ↓ 6.4Hz,
 OCH₂CH), 3.23 (1H, dd, ↓ 11.5, 7.4Hz, CHCHAHBS), 3.05 (1H, dd, ↓
 11.0, 5.4Hz, CHCHAHBSAr), 2.89 (2H, m, CHCHAHBS + CHCHAHBSAr),
 10 21.87 (1H, m, CHMe₂), 0.90 (3H, s, Me) and 0.88 (3H, s, Me). m/z (ESI,
 60V), 487 (M⁺⁺ 1).

EXAMPLE 61**N-(3,4,5-Trimethoxyphenyl)acetyl-D-thioproline-(O-benzyl)-L-tyrosine**

δH (DMSO-d⁶, 390K) 7.74 (1H, br s, NH), 7.42-7.29 (5H, m, Ar-H), 7.12
 15 (2H, ABd, ↓ 8.6Hz, ArH), 6.90 (2H, ABd, ↓ 8.6Hz, Ar-H), 6.54 (2H, s,
 MeO₃-Ar-H), 5.06 (2H, s, CH₂OPh), 4.89 (1H, m, CHα-thiopro), 4.83 (1H,
 d, ↓ 9.2Hz, NCHAHBS), 4.49 (1H, m, CHαtyr), 4.38 (1H, d, ↓ 9.2Hz,
 NCHAHBS), 3.72 (6H, s, OMe), 3.70 (3H, s, OMe), 3.65-3.53 (2H, m,
 20 CH₂CO), 3.25-2.86 (4H, m, CHCH₂S + CHCH₂Ar. m/z (ESI, 60V), 612
 (M⁺⁺ 1).

The following assays can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each of these

25 assays an IC₅₀ value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition of cell adhesion where 100% = adhesion assessed in the absence of the test compound and 0% = absorbance in wells that did not receive cells.

30

α₄β₁ Integrin-dependent Jurkat cell adhesion to VCAM-Ig

96 well NUNC plates were coated with F(ab)₂ fragment goat anti-human

IgG Fcγ-specific antibody [Jackson Immuno Research 109-006-098: 100 μl at 2 μg/ml in 0.1M NaHCO₃, pH 8.4], overnight at 4°. The plates were

35 washed (3x) in phosphate-buffered saline (PBS) and then blocked for 1h in PBS/1% BSA at room temperature on a rocking platform. After washing

(3x in PBS) 9 ng/ml of purified 2d VCAM-Ig diluted in PBS/1% BSA was added and the plates left for 60 minutes at room temperature on a rocking platform. The plates were washed (3x in PBS) and the assay then performed at 37° for 30 min in a total volume of 200 µl containing 2.5×10^5

5 Jurkat cells in the presence or absence of titrated test compounds.

Each plate was washed (2x) with medium and the adherent cells were fixed with 100µl methanol for 10 minutes followed by another wash. 100µl 0.25% Rose Bengal (Sigma R4507) in PBS was added for 5 minutes at room temperature and the plates washed (3x) in PBS. 100µl 50% (v/v) ethanol in PBS was added and the plates left for 60min after which the absorbance (570nm) was measured.

$\alpha_4\beta_7$ Integrin-dependent JY cell adhesion to MAdCAM-Ig

15 This assay was performed in the same manner as the $\alpha_4\beta_1$ assay except that MAdCAM-Ig (150ng/ml) was used in place of 2d VCAM-Ig and a sub-line of the β -lympho blastoid cell-line JY was used in place of Jurkat cells. The IC₅₀ value for each test compound was determined as described in the $\alpha_4\beta_1$ integrin assay.

20

$\alpha_5\beta_1$ Integrin-dependent K562 cell adhesion to fibronectin

96 well tissue culture plates were coated with human plasma fibronectin (Sigma F0895) at 5µg/ml in phosphate-buffered saline (PBS) for 2 hr at 37°C. The plates were washed (3x in PBS) and then blocked for 1h in

25 100µl PBS/1% BSA at room temperature on a rocking platform. The blocked plates were washed (3x in PBS) and the assay then performed at 37°C in a total volume of 200µl containing 2.5×10^5 K562 cells, phorbol-12-myristate-13-acetate at 10ng/ml, and in the presence or absence of titrated test compounds. Incubation time was 30 minutes. Each plate was fixed and stained as described in the $\alpha_4\beta_1$ assay above.

$\alpha_4\beta_2$ -dependent human polymorphonuclear neutrophils adhesion to plastic

35 96 well tissue culture plates were coated with RPMI 1640/10% FCS for 2h at 37°C. 2×10^5 freshly isolated human venous polymorphonuclear neutrophils (PMN) were added to th wells in a total volum of 200µl in the

presence of 10ng/ml phorbol-12-myristate-13-acetate, and in the presence or absence of test compounds, and incubated for 20min at 37°C followed by 30min at room temperature. The plates were washed in medium and 100 μ l 0.1% (w/v) HMB (hexadecyl trimethyl ammonium bromide, Sigma H5882) in 0.05M potassium phosphate buffer, pH 6.0 added to each well. The plates were then left on a rocker at room temperature for 60 min. Endogenous peroxidase activity was then assessed using tetramethyl benzidine (TMB) as follows: PMN lysate samples mixed with 0.22% H₂O₂ (Sigma) and 50 μ g/ml TMB (Boehringer Mannheim) in 0.1M sodium acetate/citrate buffer, pH 6.0 and absorbance measured at 630nm.

α IIb/ β 3-dependent human platelet aggregation

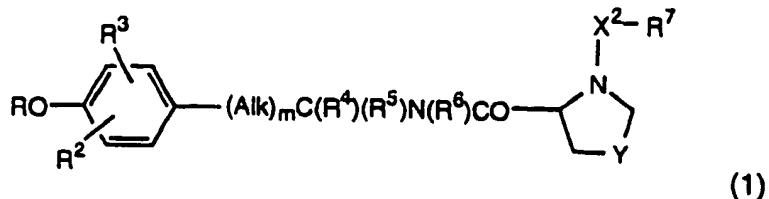
Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich plasma (PRP) was obtained by spinning fresh human venous blood anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and diluted to a cell density of 6 x 10⁸/ml in autologous plasma. Cuvettes contained equal volumes of PRP and filtered Tyrode's buffer (g/liter: NaCl 8.0; MgCl₂.H₂O 0.427; CaCl₂ 0.2; KCl 0.2; D-glucose 1.0; NaHCO₃ 1.0; NaHPO₄.2H₂O 0.065). Aggregation was monitored following addition of 2.5 μ M ADP (Sigma) in the presence or absence of inhibitors.

In the above assays the compounds of the invention generally have IC₅₀ values in the α 4 β 1 and α 4 β 7 assays of 1 μ M and below. The compounds of the Examples typically had IC₅₀ values of 500nM and below in these assays. In the other assays featuring α integrins of other subgroups the same compounds had IC₅₀ values of 50 μ M and above thus demonstrating the potency and selectivity of their action against the binding of the α 4 integrins to their ligands.

30

CLAIMS

1. A compound of formula (1):



5 wherein
 R is (1) a group R¹X¹- where R¹ is an optionally substituted alkyl or aromatic group, and X¹ is a covalent bond or a -(CH₂)_n- [where n is an integer 1 or 2], -C(O)-, -CH₂C(O)-, -NHC(O)-, -CH₂NHC(O)-, or -SO₂- group, or (2) a group (Hal¹)₃CSO₂-, where Hal¹ is a fluorine or chlorine atom;

10 R² and R³, which may be the same or different, is each a hydrogen or halogen atom or an alkyl, alkoxy, hydroxyl or nitro group;

15 Alk is an alkylene chain;

20 m is zero or an integer 1;

25 R⁴ is a hydrogen atom or a methyl group;

30 R⁵ is a group -(CH₂)_pCO₂R⁸ where p is zero or an integer 1 and R⁸ is a hydrogen atom or an alkyl group;

35 R⁶ is a hydrogen atom or an alkyl group;

40 Y is a sulphur atom or a -S(O)_q- group where q is an integer 1 or 2;

45 X² is a -C(O)-, -C(O)O-, -CONH- or -S(O)₂- group;

50 R⁷ is an optionally substituted alkyl group or an aryl or aralkyl group; and the salts, solvates and hydrates thereof.

2. A compound according to Claim 1 wherein R⁵ is a -CH₂CO₂H or -CO₂H group.

3. A compound according to Claim 2 wherein R⁵ is a -CO₂H group.

4. A compound according to any one of Claim 1 to Claim 3 wherein Y is a sulphur atom.

5. A compound according to any one of Claim 1 to Claim 4 wherein R⁴ and R⁶ is each a hydrogen atom.
6. A compound according to any one of Claim 1 to Claim 5 wherein Alk is a -CH₂- chain and m is the integer 1.
7. A compound according to Claim 1 to Claim 6 wherein R is a R¹X¹ group.
- 10 8. A compound according to Claim 7 wherein X¹ is a -CH₂- or -C(O)- group.
9. A compound according to Claim 7 or Claim 8 wherein R¹ is an optionally substituted phenyl group.
- 15 10. A compound according to any one of Claim 1 to Claim 9 wherein X² is a -C(O)- group.
11. A compound according to any one of the preceding claims wherein 20 R⁷ is an optionally substituted C₁-alkyl or benzyl group.
12. A compound according to Claim 11 wherein R⁷ is a methyl group.
13. A compound which is:
25 *N*-Acetyl-*D*-thioproline-(O-2,6-dichlorobenzyl)-*L*-tyrosine;
 N-Acetyl-*D*-thioproline-(O-2,4,6-trichlorobenzyl)-*L*-tyrosine;
 N-Acetyl-*D*-thioproline-(O-2,6-difluorobenzyl)-*L*-tyrosine;
 N-Acetyl-*D*-thioproline-(O-2,6-dichlorobenzyl)-3-nitro-*L*-tyrosine;
 N-(3-Carboxy)propionyl-*D*-thioproline-(O-2,6-dichlorobenzyl)-*L*-
30 tyrosine;
 N-Acetyl-*D*-thioproline-(O-2,4,6-trichlorobenzoyl)-*L*-tyrosine
 and the salts, solvates and hydrates thereof.
14. A pharmaceutical composition comprising a compound according to 35 Claim 1 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C07K5/06 C07D277/06 A61K38/05

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 C07K C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 394 989 A (FUJISAWA PHARMACEUTICAL CO) 31 October 1990 see the whole document	1-14
A	DATABASE WPI Section Ch, Week 9234 Derwent Publications Ltd., London, GB; Class B04, AN 92-281714 XP002076854 & JP 04 193 895 A (AJINOMOTO KK) see abstract	1-14
A	WO 97 03094 A (BIOGEN INC ;LIN KO CHUNG (US); ADAMS STEVEN P (US); CASTRO ALFREDO) 30 January 1997	1-14
A	EP 0 322 068 A (ZAMBON SPA) 28 June 1989 see claim 1	1-14
-/-		

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the IBA	Authorized officer
European Patent Office, P.B. 5818 Patentstaan 2 NL - 2260 HV Rijswijk Tel: (+31-70) 340-2040, Tx: 31 651 epo nl. Fax: (+31-70) 340-3016	Steendijk, M

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE WPI Section Ch, Week 8125 Derwent Publications Ltd., London, GB; Class 803, AN 81-451440 XP002076855 & JP 56 049 373 A (DAINIPPON PHARM CO LTD) see abstract</p> <p>-----</p>	1-14

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International Application No
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